PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Charles L. Magness
Application No.	: 09/707,576
Filed	: November 6, 2000
For	: System and Method for Selectively Classifying a Population
Examiner	: Anna Skibinsky
Art Unit	: 1631
Docket No.	: 55382-3
Date	: August 13, 2008

Attention: Board of Patent Appeals and Interferences
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPELLANT'S BRIEF (37 C.F.R. § 41.37)

Commissioner for Patents:

Appellants appeal from the final rejection of claims 1-10, 14-26, 28, 32-44 and 46-55 of the above-identified application. This Brief on Appeal is submitted in response to the Office Action of May 16, 2007, rejecting the claims, and the Advisory Action of December 20, 2007, declining to enter the amendment of November 16, 2007. The appeal is proper because the claims have been rejected twice.

The fees required under Section 1.17(c) are dealt with in the accompanying transmittal letter.

I. REAL PARTY IN INTEREST

The real party in interest in the above-identified application is Illumigen, Inc., which has its principal place of business at c/o Cubist Pharmaceuticals, Inc., 65 Hayden Avenue, Lexington, MA 02421.

II. RELATED APPEAL AND INTERFERENCES

No other appeals or interferences will directly affect, be affected by, or have a bearing on the Board of Patent Appeals and Interferences' decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 11-13, 27, 29-31, and 45 were previously cancelled. Claims 56-61 are withdrawn from consideration. Claims 1-10, 14-26, 28, 32-44 and 46-55 stand rejected and are the claims on appeal. No other claims are pending.

IV. STATUS OF AMENDMENTS

In a response filed on November 16, 2007, appellants sought to cancel claims 1-10, 14-19, 47, 49, 50 and 51 to narrow the issues, but the Examiner declined to enter that amendment, as indicated in the Advisory Action dated December 20, 2007. In the response, appellants also amended claims 20-23 and 25, but that amendment was not entered. The claims as shown in the accompanying Appendix are an accurate representation of the pending claims.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 provides a computer-implemented method for identifying a drug target associated with a selected biological condition, and is described in the specification at page 14 line 20 to page 17 line 20 and in Figures 1 and 2.

Dependent claim 2 specifies the generation of statistical data that are analyzed for classifying the population, and is described at page 3, lines 22-27.

Dependent claims 3-10 further define the classification of populations and statistical analyses, and are described at page 3, line 28 to page 4, line 9.

Dependent claims 14-19 further define the populations being analyzed as ARA, ARU, and URU. These are defined at page 3, lines 22-27; page 6, lines 5-16; page 19, lines 10-17; and page 30, lines 10-23.

Appellants previously sought to cancel claims 1-10 and 14-19. Independent claim 20 provides a computer-implemented method of data analysis for identifying a

target for use in treating a selected biological condition. Claim 20 is described at page 14, line 20 to page 17, line 20 and Figures 1 and 2.

Dependent claims 21-26 define aspects of the method in terms of how the disease characteristics, risk characteristics, and status are categorized to identify a target, and are supported at page 5, line 24 to page 6, line 4.

Dependent claim 28 provides that the medical histories of the subjects are compared with the medical test results of the groups. The claim is supported at page 30, lines 24-28.

Dependent claims 31-40 further define how targets are identified, how subjects are classified, and what test results are used. The claims are supported at page 32, line 13 to page 34, line 16.

Independent claim 41 provides a system for data analysis to identify a target for treating a selected biological condition, as supported at page 14, lines 20-28 and Figure 1. Dependent claims 42-46 further define actions of the processor of claim 41 in relation to numerical scores and data, as supported at page 6, lines 17-26; page 19, lines 10-17, and page 30, lines 10-23.

Dependent claims 47-51 depend from claim 1 or 20, and provide specific embodiments of the method in relation to identifying a target. Claim 47 provides identifying a drug target (page 13, lines 16-20). Claim 48 provides identifying a diagnostic assay (page 34, lines 11-16). Claim 49 provides identifying a vaccine (page 34, lines 11-16). Claims 50 and 51 provide identifying a candidate drug (page 5, lines 14-18).

Claims 52-55 depend from claim 41, and provide for identifying a drug target, a candidate drug, a diagnostic assay, and a vaccine. (Page 34, lines 10-18; page 34, lines 11-16.)

Appellants previously sought to cancel claims 29-61.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Did the Examiner err by failing to withdraw the finality of the Office Action dated May 16, 2007 when that Action did not comply with the M.P.E.P. section governing final rejection language?

II. Did the Examiner err by rejecting claims 1-19, 47, 49, 50 and 51 for allegedly being directed to non-statutory subject matter, when appellants previously amended these claims as suggested by the Examiner, to address the Examiner's ground of rejection?

III. Did the Examiner err by rejecting claims 1-10, 14-26, 28, 31-44, and 46-55 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement, because the claims as amended are enabled, as attested to by three experts?

VII. ARGUMENTS

Introduction

Prosecution of this application has now lasted almost eight years since it was filed on November 6, 2000. The application has been transferred between Examiners, causing progress made with one Examiner to be lost when the next Examiner effectively started over. Several personal interviews have been held, and many rounds of Office Action and Amendment are of record. Affidavits of experts have been carefully prepared and filed. The history is summarized below.

The application had been pending for three years when the undersigned conducted a personal interview with Examiner C. Michelle Colon and Supervisory Examiner Tariq Hafiz. The interview was intended to serve as an overview of the invention, and to establish communication going forward.

A first action was mailed on June 16, 2004, and raised issues under 35 U.S.C. §§ 101, 102(e), and 103. There were no § 112 rejections. On August 26, 2004, appellants conducted a telephonic interview with Examiner Colon. The Examiner suggested amendment to the claims to clarify claim language. Appellants filed a response on September 13, 2004. The claims were amended as discussed with the Examiner, and arguments were made to address the prior art rejections.

A second and final Office Action was mailed on January 3, 2005. The 35 U.S.C. § 101 rejection was withdrawn in view of the claim amendments, and the prior art rejections were withdrawn. A new rejection under 35 U.S.C. § 102(a) was asserted

over five "risk assessment" articles published by the NIH, despite the action being final. The previous prior art rejections under §§ 102(e) and 103 were not retained.

On March 28, 2005, appellants further amended the claims to address an informality, and argued that the claims were not anticipated by the NIH references cited under 35 U.S.C. § 102(a).

On April 8, 2005, the Examiner issued an Advisory Action stating that the proposed amendment raised new issues requiring further search and consideration.

Appellants filed a request for continuing application, and the amendment filed on May 2, 2005 was entered. The case had been transferred to Examiner Anne Skibinsky and Supervising Examiner Ardin Marschel. An Office Action was mailed on August 29, 2005. The Examiner stated that claims 1-10, 14-26, 28, 31-44 and 46-55 (all the pending claims) contained new matter, and rejected them under 35 U.S.C. § 112, written description and enablement. The rejection of claims 1-10, 14-26, 28, 31-44, and 46-55 under 35 U.S.C. § 102(a) over the NIH publication was maintained.

A response was filed on February 24, 2006. Appellants amended the claims to address individually each of the Examiner's points about claim language. Table 1 at pages 19-21 of the amendment provides precise support in the specification for each term that the Examiner questioned.

Appellants addressed the enablement rejection by discussing the *Wands* factors. *In re Wands*, 8 U.S.P.Q. 2d 1400, 1404 (Fed Cir. 1988). In support of particular factors, appellants submitted an Affidavit of an expert. Dr. Shawn Iadonato's affidavit attested to the amount of direction or guidance provided. According to Dr. Iadonato, when the guidance in the specification was followed, a target and drug for treating hepatitis C were identified. This affidavit also contested the Examiner's statement that the discovery of one drug target costs hundreds of millions of dollars and several years of research time.

Regarding the rejection under 35 U.S.C. § 102(a) (NIH publication), appellants explained in detail how the claim language distinguished the inventive methods from the cited art methods.

In an Office Action dated June 16, 2006, the Examiner withdrew new claims 56-61 from consideration. Regarding the grounds of rejection, the affidavit of Dr. Shawn

Iadonato was deemed insufficient to overcome the enablement rejection because (a) Dr. Iadonato was said to be of extraordinary skill in the art; (b) the affidavit did not establish when the experiments were performed; (c) a URU population wasn't mentioned in the independent claims; and (d) the affidavit only supported identification of a drug target for hepatitis C.

Claims 1-19, 47, 49, 50 and 51 were rejected under 35 U.S.C. § 101 as the claims allegedly were directed to non-statutory subject matter. At the sentence bridging pages 4-5, the Examiner seemed to offer a remedy:

> An example which would make the instant method steps statutory would be to include a step of displaying the data for a user. Hence, the data would become concrete, tangible, and useful. (Emphasis added.)

Claims 1-10, 14-26, 28, 31-44, and 46-55 were rejected under 35 U.S.C. § 112, first paragraph, enablement.

The following rejections were withdrawn:

a. Rejection under 35 U.S.C. § 112, second paragraph, vague and indefinite.

b. Rejection under 35 U.S.C. § 102 over the NIH risk assessment models.

At this stage, appellants had narrowed the issues to rejections for (a) lack of utility (for which the Examiner had offered remedial language) and (b) lack of enablement. The next amendment was prepared for addressing these remaining issues, and it was filed on December 18, 2006.

Appellants amended claim 1 to recite a step of displaying the data for a user – language suggested by the Examiner. Support in the specification was indicated.

In response to the enablement rejection – the only other remaining rejection – appellants submitted three affidavits of experts. Appellants addressed each of the Examiner's comments individually and thoroughly. The experts are discussed below.

Expert 1, Dr. Cammie Lesser. Dr. Cammie Lesser is an internationally recognized scientist and physician employed as Assistant Professor at Massachusetts General Hospital/Harvard Medical School in Cambridge, Massachusetts. She received a Bachelors Degree in Biochemistry from Brown University, a Ph.D. degree in Biochemistry in 1993 from the University of California at San Francisco, and an M.D. degree in 1995 from the University of California at San Francisco. She is an author or

co-author of several peer-reviewed research articles and has been invited to give presentations on her research at national and international meetings. Prior to joining Massachusetts General Hospital/Harvard Medical School, she was a medical resident at the University of Washington.

Expert Dr. Cammie Lesser attested that the application provides a "very effective short-cut to drug target discovery." She also attested that the methods in the application are distinguished from current methods of target and drug discovery. She stated that she understood the meanings and implications of the terms employed, including the "at risk unaffected" (ARU) group. In paragraph 5, she concluded that as a medical doctor, she found it to be routine to identify "at risk unaffected" and "at risk affected" populations, and to obtain biological samples from these populations. At paragraphs 7-11, she refutes specific statements of the Examiner in concluding that she finds the application to be enabling for the claims.

Expert 2, Dr. Richard Myers. Dr. Richard Myers is an internationally recognized scientist employed as Chairman of the Department of Genetics, Stanford University School of Medicine. He also holds positions as Stanford W. Ascherman Professor of Genetics, and Director, Stanford Human Genome Center, both in the Department of Genetics at Stanford University School of Medicine.

He received a Bachelors Degree in Biochemistry in 1977 from the University of Alabama, and a Ph.D. degree in Biochemistry in 1982 from the University of California at Berkeley. In addition to authoring or co-authoring over 130 peer-reviewed research articles, Dr. Myers has received awards relating to his work in genetics and the human genome, including the Wills Foundation Award, 1986-2005; the Pritzker Foundation Award, in 2002, and the Searle Scholar Program, from 1987-1990. Dr. Myers disclosed in his affidavit that he served on the Scientific Advisory Board of Illumigen Biosciences, Inc. at the time of signing the affidavit.

Expert Dr. Richard Myers attested to several factors that demonstrate enablement of the claimed invention. With his expertise in genetics, he stated that much of the genetics work that the Examiner deemed non-enabled was routine (Myers affidavit, paragraph 4.) He also stated that if the claimed methods were followed, it would not require years to complete the identification of a drug target. (Paragraph 5.)

He further stated that it is possible and routine to identify a mutation without knowledge of the underlying disease mechanism. (Paragraph 6.) In paragraphs 8-12, he specifically addressed and refuted individual statements of the Examiner that related to the alleged lack of enablement.

Expert 3, Dr. Shawn Iadonato. Appellants submitted a new affidavit of Dr. Shawn Iadonato, who is also a co-inventor. Dr. Iadonato received a Bachelors Degree in Biology from the University of Pennsylvania in Philadelphia and a Ph.D. degree in Genetics from the University of Washington. He is an author or co-author of numerous peer-reviewed research articles and has been invited to give numerous presentations on his research at national and international meetings.

Dr. Iadonato managed sequence data collection for the University of Washington Genome Center. He subsequently served as Founder, Vice-President, and Chief Scientific Officer of Illumigen Biosciences, Inc., the applicant and assignee of the present patent application. In that capacity, he managed the scientific and drug development programs of Illumigen. He has more than ten years experience developing and managing large-scale genetics and genomics projects, most notably involving his work on the Human Genome Project.

The Examiner had deemed Dr. Iadonato to be of "extraordinary" skill. In recognition of the Examiner's position on this, Dr. Iadonato's new affidavit was careful to focus on enablement issues he was uniquely qualified to evaluate. He stated that the first time the claimed methods were followed, they led to discovery of a mutation that correlated with resistance to hepatitis C.

At this stage, appellants had made a thorough and *bona fide* attempt to alleviate all the Examiner's remaining concerns, including adding claim language suggested by the Examiner.

It was therefore a surprise to receive the Office Action dated May 16, 2007 wherein the Examiner maintained the rejection under 35 U.S.C. § 101. The Examiner also maintained the rejection under 35 U.S.C. § 112, first paragraph, enablement, despite the careful and thoughtful affidavits, to which the experts devoted substantial personal time and effort.

The Examiner cited numerous reasons why she found the expert affidavits to be unpersuasive. The Examiner focused on very specific wording in the affidavits and found that that precise wording was not mirrored in the claims. Appellants submit that experts expressed complex scientific concepts in their own words, and it is important to look at the meaning, not to focus on minor variations in language.

The Examiner also substituted her opinion for the experts' statements. As one example, at page 18, lines 5-6, regarding the affidavit of Dr. Myers, she states, "[d]etermining which of these is a 'drug target' requires undue experimentation as one skilled in the art would have to guess at which is truly causative of disease symptoms, and would have to perform further research to confirm that guess." This completely disregards the expert opinion of a scientist who makes his living evaluating how much experimentation would be needed to conduct a successful research project. The Examiner addresses that incongruity by stating that Dr. Myers' extensive experience in evaluating grant proposals is not equivalent to predicting success of a research project, then she extends that to dismissing Dr. Myers' ability to evaluate enablement of a claimed invention. (Page 16, lines 6-10.)

Regarding the affidavit of Cammie Lesser, M.D., Ph.D., the Examiner chooses to disagree with Dr. Lesser's expert opinion on what experimentation is routine. See page 22, lines 4-5 of the Office Action, "[t]he Examiner maintains that this is not routine and represents undue experimentation." Appellants submit that it is not the Examiner's role to substitute her opinion for that of Dr. Lesser.

Regarding the affidavit of Dr. Iadonato, the Examiner seems to acknowledge that a drug was in fact identified in short time using the claimed methods (Office Action, page 24, lines 14-16); she nevertheless finds fault with the affidavit because Dr. Iadonato does not use language that is identical to the claim language. For example, see page 24, lines 7-11: by stating "studying ARU populations who already express a version of the drug," Dr. Iadonato was using language intended to be readily understood, yet equivalent to the claim language cited by the Examiner, "identification of a drug target based on genetic variations between broadly defined populations."

The fact of the discovery of a promising treatment for hepatitis C using the claimed methods has been dismissed by the Examiner as not supportive of enablement.

Appellants submit that reduction of the claimed method to actual practice, and high valuation of the resulting product by the pharmaceutical industry, are strong indicia that the claims are in fact enabled as attested to by highly qualified experts.

The Examiner also made the action final but failed to include the "final action" language as provided by the M.P.E.P. This is discussed in Argument I herein.

Appellants at that stage were highly motivated to move the application forward. In a response filed on November 16, 2007, they canceled claims 1-12, 14-19, 31-44, and 46-61. This rendered moot the rejection under 35 U.S.C. § 101, and clearly signaled appellants' desire to resolve the issues without further prolonged prosecution. At this point, the case had been pending for seven years.

Appellants further amended the claims to address the remaining issues. Only eight claims remained: claims 20-26 and 28. However, instead of working with appellants to resolve the issues for this significantly reduced claim set, the Examiner neither withdrew the finality as requested, nor did she consider the short amendment, which only had five pages of remarks.

On December 20, 2007, an Advisory Action was mailed. The amendments to the claims were deemed to introduce a substantive change requiring further search and consideration.

Appellants filed a Request for a Pre-Appeal Brief Review, and in a Notice mailed on May 6, 2008, the Panel stated that the case was in condition to proceed to the Board of Patent Appeals and Interferences. This appeal therefore follows.

While this application has been pending, the disclosed invention has led a successful life, both scientific and commercial, in the laboratory and in industry, and the first product of the inventive method is heading for the clinic. The original assignee, Illumigen Biosciences Inc., was acquired by Cubist Pharmaceuticals, Inc., on December 24, 2007, in part on the strength of the drug target whose discovery is discussed in the expert affidavits that the Examiner found to be unpersuasive. An IND for the lead compound is expected to be filed in 2008.

That compound, a polypeptide, was identified by appellants as a variant protein produced by ARU populations who were resistant to hepatitis C infection despite repeated exposure. The *phenotype* of these ARU populations differ from the phenotype

of the matched ARA populations (exposed to hepatitis C and infected), and the differing *genotypes* is manifested by production of the variant protein that itself is the therapeutic agent. This represents a real-life embodiment of the claims. A copy of the press release is submitted herein as Exhibit 5. (It was not previously of record because the acquisition of Illumigen Biosciences, Inc. took place after appellants filed the most recent amendment, on November 16, 2007.)

This Brief on Appeal is filed to seek the Board's position on the prosecution and to direct the case to allowance, or to clarification of the issues so that appellants can address those issues in a manner that moves the case forward, not backward.

I. Did the Examiner err by failing to withdraw the finality of the Office Action dated May 16, 2007? Although the box was checked indicating that the May 16, 2007 Office Action was final, that Office Action failed to include the proper paragraph as provided for in M.P.E.P.:

> 7.39 Action is Final
>
> THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy set forth in 37 CFR 1.136(a).
>
> A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Because the paragraph was not included in the May 16, 2007 Office Action, appellants were not given the notice regarding deadlines, and the simple checking of a box could have been a clerical error, not the Examiner's decision.

Appellants urged that the Examiner withdraw the finality. This was especially requested under the circumstances of the November 16, 2007 amendment cancelling most of the claims and significantly narrowing the issues which the Examiner had to

consider prior to issuing the next communication, which appellants submit should not have been an Advisory Action refusing to enter an amendment that clearly was positioning the case for allowance or at least for negotiation with the Examiner on any remaining points of claim language.

Appellants therefore argue that the finality should be withdrawn and the November 16, 2007 amendment be entered.

Appellants attempted to cancel claims 1-10, 14-19, 47, 49, 50, and 51 in the amendment filed November 16, 2007. Since the Examiner refused to enter the amendments, the claims remain pending. Cancelling claims 1-10, 14-19, 47, 49, 50, and 51 would have rendered moot the rejection under 35 U.S.C. § 101.

II. Did the Examiner err by rejecting claims 1-19, 47, 49, 50 and 51 under 35 U.S.C. § 101?

With regard to the claim rejections under 35 U.S.C. § 101, appellants respectfully submit that in the Office Action dated June 16, 2006, the Examiner suggested that this rejection could be overcome by, "includ[ing] a step of displaying the data for a user. Hence, the data would become concrete, tangible, and useful." See page 5, Office Action dated June 16, 2006.

Claim 1 was amended to read as follows(the entire claim is found in the Claims Appendix) :

> 1. (Currently Amended) A computer-implemented method for the identification of a drug target associated with a selected biological condition, comprising:
>
> [lines omitted for brevity]
>
> performing a computer analysis of genetic data from the ARA sub-population and the ARU sub-population to identify genetic variations therebetween;
>
> and displaying each of the identified target candidate genes to a user...

The support for the amendment to recite displaying identified target candidate genes to a user is found throughout the description of Figure 1 at page 15, line 3 to page 16, line 8, as well as page 17, lines 1-3.

Despite appellants' amendment to the claims reciting a step of displaying the data for a user in the response to the June 16, 2006 Office Action, this rejection has been maintained. See pages 3 and 16, response dated December 18, 2006, and in the May 16, 2007 Office Action. Thus, appellants respectfully submit that this rejection should be withdrawn.

III. Did the Examiner err by rejecting claims 1-10, 14-26, 28, 31-44 and 46-55 under 35 U.S.C. § 112, first paragraph? Appellants respectfully submit that the Examiner has failed to adequately consider the originally filed application as well as the expert affidavits previously filed. Appellants submit that no undue experimentation is required to practice the presently pending claims. Affidavits by Drs. Lesser and Myers in support of the claims are of record. See pages 17-26 (and corresponding affidavits) of the amendment filed December 18, 2006. An affidavit of Dr. Iadonato, filed with a Supplemental Response dated February 22, 2007, was of record.

Appellants submit that each point of the Examiner's rejections had been addressed in previous responses. The claims relate to a computer-implemented method for identification of a drug target associated with a selected biological condition, comprising: using a computer to analyze stored data related to medical histories of a population; using a computer to analyze stored data related to medical test results for the population; and based on computer analysis of the data related to the medical histories and the data related to the medical test results, classifying the population into at least two phenotypic sub-populations.

These sub-populations are defined as at risk and affected (ARA), whose members have ever been affected by the selected biological condition, and at risk and unaffected (ARU), whose members ought to be affected by the selected biological condition at the present time based on a risk analysis, but are unaffected by the selected biological condition at the present time. The steps further include: performing a computer analysis of genetic data from the ARA sub-population and the ARU sub-population to identify genetic variations therebetween; displaying the data for a user; and using data related to the identified genetic variations between the ARA sub-population and the ARU sub-population to identify the drug target associated with the selected biological condition.

An element of the present invention is that prior knowledge of the genetic basis of a disease is not required for identification of a drug target. As set forth at line 22, page 10 – line 25, page 11 of the originally filed application, population members may be classified according to phenotype, and further characterized by genotype. In prior art techniques, the disease itself is studied by analyzing the defective genes and proteins of people afflicted with the disease or condition. In the present disclosure, by contrast, drug targets are identified through the use of ARU (at risk, unaffected) populations to discover the phenotype of people who are naturally resistant to the disease or condition. The differences that are found in the unaffected population become the basis of the treatment for that disease.

Figures 3-5 of the originally filed application illustrate the methods for defining the epidemiological ARA and ARU populations, as well as testing the sub-populations. A candidate drug target (whether a small molecule, polynucleotide, polypeptide, antibody, or other biological or chemical target) is determined based on the identification of the genetic differences in the phenotypically defined populations and/or sub-populations. In most cases, the target is easily discernible, for example, the case where a genetic difference causes one at-risk group of individuals to be unaffected but another at-risk group of individuals is affected.

For such a case, the person of skill in the art need only to identify the biological manifestation of the genetic difference, whether it is an increase, a decrease, or a change in the protein encoded by or regulated by the identified mutations. Without regard to the outcome of this last step, as soon as the target has been identified by the presence of mutations that associate with the ARU versus the ARA group, then the presently pending claims have been achieved. See for example, page 17, line 21, page 21, line 13, page 25, line 18, and page 30, line 8, of the originally filed application.

Expert affidavits were filed in support of appellants' statements. The Examiner did not afford the expert affidavits "meaningful consideration," as required under *In re Sullivan*, 498 F.3d 1345, 1356 (Fed. Cir. 2007). In *Sullivan*, the court stated that the declarations supported the applicants' arguments, and had the Board considered or reviewed the submitted declarations in any meaningful way, it might have come to a

different conclusion than it otherwise had. *Id.* Thus, when a patent applicant puts forth rebuttable evidence, the Board must consider that evidence.

Appellants respectfully submit that the Affidavits attest that use of the presently pending claims does result in identification of candidate drug targets, as exemplified by the identification of drug targets related to hepatitis C. In fact, candidate drug targets identified by the presently pending claims have resulted in discovery of a therapeutic polypeptide as an anti-viral therapy for hepatitis C. This therapeutic polypeptide is moving towards clinical trial. Thus, the testimony presented in the Affidavits confirms that the presently pending claims are fully enabled by the instant application.

Appellants submit that the claim amendments intended to overcome the § 112, first paragraph rejection were improperly refused entry, as a new search would not have been necessary if the amendment filed on November 16, 2007, were entered. The amendment focused the claims on one specific category ("disease") out of a previously searched defined group ("biological condition"), as set forth in the application, for example, at page 8 of the originally filed specification. Appellants further note that, even prior to the amendment of November 16, 2007, claim 20 included the step of "defining disease characteristics," including medical tests, and risk characteristics. Likewise, dependent claim 23 recited specific "disease characteristics."

In conclusion, appellants request that the Board direct the entry of the amendment filed on November 16, 2007, and allowance of claims 20-26 and 28. These claims represent a small subset of the currently pending claims. They have been amended on several occasions to comply with numerous Office Actions that represent the views of two different Examiners. Extensive work and thought have gone into being completely responsive to these Examiners, and appellants would like the patent application to be allowed. If allowance is not possible at this stage, appellants ask for the Board's guidance on how to make the claims compliant with any remaining grounds for rejection, so that a patent may be granted that protects appellants' ongoing commercial efforts at a U.S.-based company, and substantial personal and financial investment.

Commissioner is hereby authorized to charge the required Appeal fee of $500, to Deposit Account No. 04-0258. If additional fees are believed necessary, the

Commissioner is further authorized to charge any deficiency or credit any overpayment to Deposit Account No. 04-0258.

Respectfully submitted,
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VIII. APPENDIX OF CLAIMS INVOLVED IN THE APPEAL

1. A computer implemented method for the identification of a drug target associated with a selected biological condition, comprising:

using a computer to analyze stored data related to medical histories of a population;

using a computer to analyze stored data related to medical test results for the population; and

based on computer analysis of the data related to the medical histories and the data related to the medical test results, classifying the population into at least two phenotypic sub populations defined as

at risk and affected (*ARA*), whose members have ever been affected by the selected biological condition, and

at risk and unaffected (*ARU*), whose members ought to be affected by the selected biological condition at the present time based on a risk analysis, but are unaffected by the selected biological condition at the present time;

performing a computer analysis of genetic data from the ARA sub population and the ARU sub population to identify genetic variations therebetween;

displaying the data for a user; and

using data related to the identified genetic variations between the ARA sub population and the ARU sub population to identify the drug target associated with the selected biological condition.

2. The method of claim 1, further comprising generating statistical data related to the medical histories and the medical test results wherein classifying the population comprises analyzing the statistical data.

3. The method of claim 1 wherein analyzing medical histories comprises assigning numerical scores to selected conditions associated with the selected biological condition.

4. The method of claim 1 wherein analyzing medical test results comprises assigning numerical scores to selected medical tests associated with the selected biological condition.

5. The method of claim 1 wherein analyzing medical histories and medical test results comprises assigning numerical scores to selected conditions associated with the selected biological condition and analyzing medical test results comprises assigning numerical scores to selected medical tests associated with the selected biological condition.

6. The method of claim 5 wherein classifying the population comprises evaluating the numerical scores for the medical histories and the medical test results.

7. The method of claim 6 wherein classifying the population comprises combining the numerical scores for the medical histories and the medical test results and classifying the population based on the combined numerical scores.

8. The method of claim 5, further comprising generating statistical data related to the numerical scores for the medical histories and the medical test results wherein classifying the population comprises analyzing the statistical data.

9. The method of claim 8 wherein the statistical data comprises generating a frequency distribution plot related to the numerical scores for the medical histories and the medical test results.

10. The method of claim 1, further comprising comparing the medical histories and the medical test results of the sub population classified as *ARU* with the medical histories and the medical test results of the sub population classified as *ARA*.

11-13 (Cancelled)

14. The method of claim 1, further comprising selecting the portion of the sub population classified as *ARA* and using the selected portion as a control group.

15. The method of claim 1 wherein classifying the population further comprises classifying the population into the ARA sub population, the *ARU* sub population or a phenotypic sub population defined as unknown risk and unaffected (*URU*) by the selected biological condition.

16. The method of claim 15, further comprising comparing the medical histories and the medical test results of the sub population classified as *ARU* with the medical histories and the medical test results of the sub population classified as *URU*.

17. The method of claim 15 wherein the medical test results comprises genetic test results, the method further comprising comparing the genetic test results of

the sub population classified as *ARU* with the genetic test results of the sub population classified as *URU*.

18. The method of claim 17, further comprising determining genetic differences between genetic test results of the sub population classified as *ARU* with the genetic test results of the sub population classified as *URU*.

19. The method of claim 18, further comprising identifying drug targets based on the genetic differences between genetic test results of the sub population classified as *ARU* with the genetic test results of the sub population classified as *URU*.

20. A computer implemented method of data analysis to identify a target for use in treating a selected biological condition, comprising:

defining disease characteristics of the selected biological condition, including medical tests associated with the selected biological condition;

performing a computer analysis of medical test results based on medical tests performed on biological samples from a plurality of subjects with respect to the defined characteristics of the selected biological condition;

based on the analysis, determining an affected status of each of the plurality of subjects;

defining risk characteristics of the selected biological condition;

based on the risk characteristics, determining a risk status of each of the plurality of subjects;

based on the affected status and the risk status, classifying each of the plurality of subjects into a predetermined category for the selected biological condition selected from a group comprising at risk, affected (ARA), whose members have ever been affected by the selected biological condition, and at risk, unaffected (ARU), whose members remain unaffected by the selected biological condition and whose unaffected status is inconsistent with the risk status;

performing genetic tests on the plurality of subjects;

analyzing the genetic test results of the group of subjects classified as ARU with the genetic test results of the group of subjects classified as ARA to determine genetic differences between genetic test results of the group of subjects classified as ARU with the genetic test results of the group of subjects classified as ARA; and

identifying one or more targets for use in treating the selected biological condition.

21. The method of claim 20 wherein the defined disease characteristics of the selected biological condition have associated numerical scores and determining the affected status of each of the plurality of subjects comprises determining numerical scores based on the analysis of the medical test results.

22. The method of claim 20 wherein the defined risk characteristics of the selected biological condition have associated numerical scores and determining the risk status of each of the plurality of subjects comprises determining numerical scores.

23. The method of claim 20 wherein the defined disease characteristics of the selected biological condition have associated numerical scores and the defined risk characteristics of the selected biological condition have associated numerical scores, the classification of each of the plurality of subjects into a predetermined category being based on the numerical scores for affected status and risk status.

24. The method of claim 23 wherein the numerical scores for affected status and risk status are combined to form a combined numerical score, the classification of each of the plurality of subjects into a predetermined category being based on the combined numerical scores for affected status and risk status.

25. The method of claim 20 wherein the medical tests associated with the selected biological condition have varying degrees of relevance in defining the disease characteristics, the method further comprising assigning relevance weighting factors to the medical tests based on the degree of relevance, the affected status being based on the weighted medical tests.

26. The method of claim 20, further comprising generating statistical data related to the affected status and risk status wherein classifying each of the plurality of subjects into a predetermined category comprises analyzing the statistical data.

27. (Cancelled)

28. The method of claim 20 wherein risk status is determined at least in part from medical histories of the plurality of subjects, the method further comprising comparing the medical histories and the medical test results of the group of subjects

classified as *ARU* with the medical histories and the medical test results of the group of subjects classified as *ARA*.

29-30. (Cancelled)

31. The method of claim 20 wherein identifying one or more targets comprises identifying a drug target based on the genetic differences between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *ARA*.

32. The method of claim 20 wherein identifying one or more targets comprises identifying a diagnostic assay based on the genetic differences between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *ARA*.

33. The method of claim 20 wherein identifying one or more targets comprises identifying a vaccine based on the genetic differences between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *ARA*.

34. The method of claim 20 wherein the plurality of subjects are classified into a category selected from a group comprising at risk, affected (*ARA*), unknown risk, unaffected (*URU*), and at risk unaffected (*ARU*).

35. The method of claim 34 wherein risk status is determined at least in part from medical histories of the plurality of subjects, the method further comprising comparing the medical histories and the medical test results of the group of subjects classified as *ARU* with the medical histories and the medical test results of the group of subjects classified as *URU*.

36. The method of claim 34 wherein the medical test results comprises genetic test results, the method further comprising comparing the genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *URU*.

37. The method of claim 36, further comprising determining genetic differences between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *URU*.

38. The method of claim 37, further comprising identifying a drug target based on the genetic differences between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *URU*.

39. The method of claim 38, further comprising identifying a diagnostic assay based on the genetic differences between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *URU*.

40. The method of claim 38, further comprising identifying a vaccine based on the genetic differences between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *URU*.

41. A system for data analysis to identify a target for treating a selected biological condition, comprising:

a affected status data structure containing numerical data defining disease characteristics of the selected biological condition, including medical tests associated with the selected biological condition;

a disease risk data structure containing numerical data defining disease risk characteristics of the selected biological condition; and

a processor to:

accept medical test results from a plurality of subjects and assign affected status numeric scores to the medical test results based on the numerical data defining disease characteristics of the selected biological condition;

store the affected status numeric scores for each of the subjects in the affected status data structure;

accept medical history data from a plurality of subjects and assign current disease risk numeric scores to the medical history data based on the numerical data defining disease risk characteristics of the selected biological condition;

store the disease risk numeric scores for each of the subjects in the disease risk data structure;

determine an affected status and risk status for each of the subjects based on the respective affected status numeric scores and the current disease risk numeric scores:

based on the affected status and the risk status, classify each of the plurality of subjects into a predetermined category selected from a group of categories comprising at risk, affected (ARA) and at risk unaffected (ARU);

analyze genetic test result data to determine genetic differences between the subjects in the ARA category and subjects in the ARU category; and

identify a target for treating the selected biological condition.

42. The system of claim 41 wherein the processor combines the numerical scores for affected status and risk status to form a combined numerical score, the processor further classifying of each of the plurality of subjects into a predetermined category being based on the combined numerical scores for affected status and risk status.

43. The system of claim 41 wherein the medical tests associated with the selected biological condition have varying degrees of relevance in defining the disease characteristics, the processor further assigning relevance weighting factors to the medical tests based on the degree of relevance, the processor determining the affected status based on the weighted medical tests.

44. The system of claim 41 wherein the processor further generates statistical data related to the affected status and risk status, the processor further classifying of each of the plurality of subjects into a predetermined category being based on the combined numerical scores for affected status and risk status based on analysis of the statistical data.

45. (Cancelled)

46. The system of claim 41 wherein the processor further classifies each of the plurality of subjects into a predetermined category selected from a group of categories comprising at risk, affected (*ARA*), unknown risk, unaffected (*URU*), and at risk unaffected (*ARU*).

47. The method of claim 1 wherein identifying a target comprises identifying a drug target based on the genetic variations between genetic test results of the group of

subjects classified as *ARU* with the genetic test results of the group of subjects classified as *ARA*.

48. The method of claim 1 wherein identifying a target comprises identifying a diagnostic assay based on the genetic variations between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *ARA*.

49. The method of claim 1 wherein identifying a target comprises identifying a vaccine based on the genetic variations between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *ARA*.

50. The method of claim 1 wherein identifying a target comprises identifying a candidate drug based on the genetic variations between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *ARA*.

51. The method of claim 20 wherein identifying a target comprises identifying a candidate drug based on the genetic variations between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *ARA*.

52. The system of claim 41 wherein the processor is configured to identify a drug target based on the genetic variations between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *ARA*.

53. The system of claim 41 wherein the processor is configured to identify a candidate drug based on the genetic variations between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *ARA*.

54. The system of claim 41 wherein the processor is configured to identify a diagnostic assay based on the genetic variations between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *ARA*.

55. The system of claim 41 wherein the processor is configured to identify a vaccine based on the genetic variations between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *ARA*.

56. A computer implemented method for the classification of a population for evaluation of a selected biological condition, comprising:

defining risk characteristics associated with the selected biological condition;

storing data associated with the defined risk characteristics;

defining affected status indicators for the selected biological condition;

storing data associated with the defined affected status indicators;

using the stored data to classify a study population based on the defined risk characteristics and the defined affected status indicators to thereby classify individual ones of the subjects in the study population as at risk and affected (ARA) by the selected biological condition, the ARA individuals having a risk status indicating the expectation that the individuals are at significant risk for having the selected biological condition at the present time, and an affected status indicating that the ARA individuals are presently affected by the selected biological condition, and to classify individual ones of the subjects in the study population as at risk and unaffected (ARU) by the selected biological condition, the ARU individuals having a risk status indicating the expectation that the individuals are at significant risk for having the selected biological condition at the present time, and an unaffected status indicating that the ARU individuals are presently not affected by the selected biological condition.

57. A computer implemented method for the classification of a population for evaluation of a selected biological condition, comprising:

selecting a study population to be classified into subpopulations selected from a group of subpopulations comprising:

at risk and affected (*ARA*), whose members have a risk status indicating the expectation that the members are at significant risk for having the selected biological condition at the present time, and an affected status indicating that the members of the ARA subpopulation are presently affected by the selected biological condition;

at risk and unaffected (ARU) by the selected biological condition, whose members have a risk status indicating the expectation that the members are at significant risk for having the selected biological condition at the present time, and an affected status indicating that the ARU individuals are presently not affected by the selected biological condition, and

unknown risk and unaffected (URU) by the selected biological condition, whose members have an indeterminate risk status for having the selected biological condition at the present time, and an affected status indicating that the URU individuals are presently not affected by the selected biological condition;

the size of the study population being selected so that the number of potential ARU members provides 95% confidence to detect alleles represented at at least 1% frequency in the ARU sub population; and

based on computer analysis of the data related to the medical histories and the data related to the medical test results, classifying the study population into the ARA, ARU or URU sub populations to permit evaluation of the selected biological condition by analyzing at least two of the subpopulations.

58. The method of claim 57, further comprising:

performing a computer analysis of genetic data from the ARA sub population and the ARU sub population to identify genetic variations therebetween; and

using data related to the identified genetic variations between the ARA sub population and the ARU sub population to identify a drug target associated with the selected biological condition.

59. A method for the classification of a population for evaluation of a selected biological condition, comprising:

defining risk characteristics associated with the selected biological condition;

defining affected status indicators for the selected biological condition;

classifying a study population based on the defined risk characteristics and the defined affected status indicators to thereby classify individual ones of the subjects in the study population as at risk and affected (ARA) by the selected biological condition, the ARA individuals having a risk status indicating the expectation that the individuals are at significant risk for having the selected biological condition at the present time, and

an affected status indicating that the ARA individuals are presently affected by the selected biological condition, and to classify individual ones of the subjects in the study population as at risk and unaffected (ARU) by the selected biological condition, the ARU individuals having a risk status indicating the expectation that the individuals are at significant risk for having the selected biological condition at the present time, and an affected status indicating that the ARU individuals are presently not affected by the selected biological condition, the size of the study population being selected so that the number of potential ARU members provides 95% confidence to detect alleles represented at at least 1% frequency in the ARU sub population.

60. A computer implemented method for the classification of a population for evaluation of a selected biological condition, comprising:

defining risk characteristics associated with the selected biological condition;

storing data associated with the defined risk characteristics;

defining affected status indicators for the selected biological condition;

storing data associated with the defined affected status indicators;

using the stored data to classify a study population based on the defined risk characteristics and the defined affected status indicators to thereby classify individual ones of the subjects in the study population as at risk and affected (ARA) by the selected biological condition, the ARA individuals having a risk status indicating that the individuals are expected to be affected by the selected biological condition at the present time, and an affected status indicating that the ARA individuals are presently affected by the selected biological condition, and to classify individual ones of the subjects in the study population as at risk and unaffected (ARU) by the selected biological condition, the ARU individuals having a risk status indicating that the individuals are expected to be affected by the selected biological condition at the present time, and an affected status indicating that the ARU individuals are presently not affected by the selected biological condition.

61. A computer implemented method for the identification of a population phenotypically unaffected by a selected biological condition, comprising:

defining risk characteristics associated with the selected biological condition;

storing data associated with the defined risk characteristics;

defining affected status indicators for the selected biological condition;

storing data associated with the defined affected status indicators;

using the stored data to identify individuals as phenotypically affected by the selected biological condition and to identify individuals as phenotypically unaffected by the selected biological condition despite a risk status consistent with risk status associated with individuals identified as phenotypically affected by the selected biological condition.

IX. EVIDENCE APPENDIX

Pursuant to 37 C.F.R. § 41.37(c)(1)(ix) the following evidence under 37 C.F.R. § 1.130. 1.131 or 1.132 is relied upon in this Appeal Brief.

1. Affidavit of Dr. Shawn Iadonato filed December 18, 2006. This Affidavit under 37 C.F.R. § 1.132 was made of record and considered by the Examiner. See Office Action dated May 16, 2007, page 22, lines 16-20.

2. Second Affidavit of Dr. Shawn Iadonato filed February 22, 2007. This Affidavit under 37 C.F.R. § 1.132 was made of record and considered by the Examiner. See Office Action dated May 16, 2007, page 2, lines 16-20.

3. Affidavit of Dr. Cammie Lesser dated December 15, 2006. This Affidavit under 37 C.F.R. § 1.132 was made of record and considered by the Examiner. See Office Action dated May 16, 2007, page 19, lines 20-21.

4. Affidavit of Dr. Richard Myers dated December 16, 2006 This Affidavit under 37 C.F.R. § 1.132 was made of record and considered by the Examiner. See Office Action dated May 16, 2007, page 15, lines 13-14.

5. Press release dated December 26, 2007 entitled, "Cubist Pharmaceuticals Acquires Illumigen Biosciences; Expects to File IND for Lead HCV Compound IB657 in 2008." This document is not of record because the event did not take place until after appellants filed the most recent response in the prosecution history, on November 16, 2007.

EXPRESS MAIL NO. EV737280603US

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Charles L. Magness and Shawn P. Iadonato
Application No.	:	09/707,576
Filed	:	November 6, 2000
For	:	SYSTEM AND METHOD FOR SELECTIVELY CLASSIFYING A POPULATION

Examiner	:	Anna Skibinsky
Art Unit	:	1631
Docket No.	:	55382-3
Date	:	February 24, 2006

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Affidavit of Shawn Iadonato, Ph.D. under 37 C.F.R. § 1.132

I, Shawn Iadonato, Ph.D. being duly sworn, say:

1. I am an internationally recognized scientist and at the time of filing the above-referenced patent application I was employed as Vice-President and Chief Scientific Officer, at Illumigen Biosciences, Inc., Seattle, WA. I received a Bachelors Degree in Biology from the University of Pennsylvania in Philadelphia and a Ph.D. degree from in Genetics from the University of Washington.

2. I am an author or co-author of numerous peer-reviewed research articles and have been invited to give numerous presentations on my research at national and international meetings. Prior to joining Illumigen, I managed sequence data collection

for the University of Washington Genome Center. My curriculum vitae is attached as Exhibit 1.

3. In my capacity as Founder, Vice-President, and Chief Scientific Officer, I manage the scientific and drug development programs of Illumigen. I have more than eight years experience developing and managing large-scale genetics and genomics projects, most notably involving my work on the Human Genome Project.

4. On information and belief, claims of the present application have been rejected under 35 U.S.C. § 112, first paragraph. According to the Office Action dated September 29, 2005, claims 1-10, 14-26, 28, 31-44 and 46-55 fail to comply with the enablement requirement because allegedly there is "undue experimentation required to go from the classification results achieved by implementing the invention to drug target identification without some prior knowledge of a relationship between a potential target and a biological condition as claimed." The experiments and results described in paragraphs 5-12 below support the enablement of the claimed invention by showing clearly that undue experimentation was not required to identify a drug target using the methods of the invention.

5. Illumigen's first drug is an anti-viral therapy for hepatitis C, and the drug is undergoing important pre-clinical studies; Phase I trials are scheduled for 2007. The drug was developed by following the methods as explicitly described in the present patent application.

6. In Step 1, recruiting of patients was performed from among populations at high risk for hepatitis C infection, specifically intravenous drug users and hemophiliacs. Over 3,500 subjects were screened, and a group of serially exposed and seronegative subjects was identified. These subjects correspond exactly to the ARU "at risk, unaffected" population of the claims and the specification.

7. In Step 2, we sequenced a fraction of the genome of case (ARU) and control (ARA and URU) subjects. These control subjects correspond exactly to the at

risk and affected (exposed to hepatitis C and currently infected with the virus) and unknown risk and unaffected (no exposure data and not currently infected with the virus) populations of the application and claims. Using the computer-based methods exactly as disclosed in the application, genetic association analysis was performed, and a mutation associated with the "at risk and unaffected" ARU group was identified. This mutation affects a protein which corresponds to the "target" of the claims and the specification. Thus, the target was identified solely by the computer-based analysis.

8. The mutation affects a gene involved in the interferon pathway; the gene encodes a protein known as OAS1. Using the information that mutated forms of OAS1 were expressed in the ARU group but not the ARA group, we developed an optimized form of the protein expressed by the mutated gene and tested it in an *in vitro* model of HCV infection; this protein corresponds to the therapeutic of the specification and the claims. As shown in Exhibit 2, the therapeutic protein, referred to as IB657, inhibits EMCV infection of hepatoma (Huh7) cells.

9. On information and belief, the Office Action at page 11, lines 6-8, alleges that "the method of identifying a drug target based on genetic differences between two groups is not trivial and requires years to complete..." Although I agree that identifying a drug target is not "trivial," as it in fact is a major breakthrough, I strongly disagree that it takes years to complete. By following the methods described in this application, we identified a drug target (the mutated gene OAS1) and a drug in three years from start to preclinical drug candidate. A single cycle of data input, review and analysis according to the invention led directly to this drug discovery.

10. On information and belief, the Office Action at page 7, lines 6-10, alleges that "the identification of a drug target requires knowledge of the cause of disease and the biological systems associated with it. Drug target identification currently requires several months to years of research and costs millions of dollars per drug." The operative word here is currently. What applicants have disclosed and claimed is not the current method of target and drug discovery, but new methods. The drug currently

undergoing preclinical testing, as described in paragraph 9 above, was developed at a cost of, at most, 10% of the conventional approach. Furthermore, in addition to the cost benefit, the drug has entirely different toxicity parameters. The drug is based on studying ARU populations who already express a version of the drug and enjoy the beneficial effects of having it in their system. Therefore, the drug we developed is expected to have negligible toxicity compared to traditional drugs based on synthetic chemistry approaches.

11. The drug that is the subject of paragraphs 9 and 10 above is one of many polypeptides disclosed and claimed in our subsequent co-pending patent application, Serial No. 10/972,135. That application was granted Special Status in a Decision on Petition granted on December 7, 2005. The ground for the Petition was that applicant Illumigen is a Small Entity and the subject matter of the application is a major asset of the company.

12. The Small Entity status of the company and the granting of the Petition to Make Special in the co-pending application are further evidence that the present patent application is fully enabling, because the target and the drug were discovered in less than three years through the work of far fewer employees, and using far fewer resources and expenses, as compared to drug discovery at a traditional pharmaceutical company.

I further declare that all statements made herein of my own knowledge are true and that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code.

Shawn Iadonato, Ph.D.

State of Washington)
) ss.
County of *King*)

On this 22nd day of February, 2006, before me, a Notary Public in and for the State and County aforesaid, personally appeared Shawn Iadonato, Ph.D. to me known and known to me to be the person of that name, who signed and sealed the foregoing instrument, and he acknowledged the same to be his free act and deed.

Notary Public SHANNON ELISE LEIGHTON
MY APPOINTMENT EXPIRES: 5-25-06

Commission expires_____

EXPRESS MAIL NO.
EB 069600865 US

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Charles L. Magness and Shawn P. Iadonato
Application No.	:	09/707,576
Filed	:	November 6, 2000
For	:	SYSTEM AND METHOD FOR SELECTIVELY CLASSIFYING A POPULATION

Examiner	:	Anna Skibinsky
Art Unit	:	1631
Docket No.	:	55382-3
Date	:	February 9, 2007

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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I, Shawn Iadonato, Ph.D. being duly sworn, say:

1. I am an internationally recognized scientist and at the time of filing the above-referenced patent application I was employed as Vice-President and Chief Scientific Officer, at Illumigen Biosciences, Inc., Seattle, WA. I received a Bachelors Degree in Biology from the University of Pennsylvania in Philadelphia and a Ph.D. degree in Genetics from the University of Washington.

2. I am an author or co-author of numerous peer-reviewed research articles and have been invited to give numerous presentations on my research at national and international meetings. Prior to joining Illumigen, I managed sequence data collection

for the University of Washington Genome Center. My curriculum vitae is attached as Exhibit 1.

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4. On information and belief, claims of the present application have been rejected under 35 U.S.C. § 112, first paragraph. According to the Office Action dated June 16, 2006, claims 1-10, 14-26, 28, 31-44 and 46-55 fail to comply with the enablement requirement because allegedly there is "undue experimentation required to go from the classification results achieved by implementing the invention to drug target identification without some prior knowledge of a relationship between a potential target and a biological condition as claimed." The experiments and results described in paragraphs 5-12 below support the enablement of the claimed invention by showing clearly that undue experimentation was not required to identify a drug target using the methods of the invention. In fact, following the methods of the present invention in a hepatitis C study, we found more than one drug target. The first of these was identified in an extremely short period of laboratory work (see 8. below) thus supporting the claim that the invention was sufficiently enabled.

5. Illumigen's first drug is an anti-viral therapy for hepatitis C, and the drug is undergoing important pre-clinical studies; Phase I trials are scheduled for 2007. The drug was developed by following the methods as explicitly described in the present patent application.

6. In Step 1, recruiting of patients was performed from among populations at high risk for hepatitis C infection, specifically intravenous drug users and hemophiliacs. Over 3,500 subjects were screened, and a group of serially exposed and seronegative subjects was identified. These subjects correspond exactly to the ARU "at risk, unaffected" population of the claims and the specification.

7. In Step 2, we sequenced a fraction of the genome of case (ARU) and control (ARA) subjects. These case and control subjects correspond exactly to the at risk and unaffected (exposed to hepatitis C and not currently infected with the virus) and at risk and affected (exposed to hepatitis C and currently infected with the virus) populations of the application and claims. Using the computer-based, genetic association methods like those disclosed in the application, genetic mutations associated with the "at risk and unaffected" ARU group were identified. These mutations affect a protein which corresponds to the "target" of the claims and the specification.

8. The mutations identified in step 2 of paragraph 7 above was discovered in a very short period of time with minimal resources, supporting the enablement of the methods of the invention. Illumigen's laboratory only began operation in January, 2003 and initiated DNA sequence analysis of the ARU and ARA groups in March, 2003. On October 23, 2003, a provisional application was submitted to the USPTO concerning our first drug target and detailing the primary functional mutation. The laboratory work supporting the computational genetic analysis was conducted using a single sequencing instrument and approximately one full-time-equivalent laboratory technician. Thus, while additional validating analyses were conducted after this date and drug optimization and testing has occurred over the succeeding three years, the limited amount of laboratory work that was conducted for primary identification of a drug target is highly supportive of enablement.

9. The mutation affects a gene involved in the interferon pathway; the gene encodes a protein known as OAS1. Using the information that mutated forms of OAS1 were homozygously expressed significantly more frequently in the ARU group as compared with the ARA group, we developed an optimized form of the protein derived from the mutated gene and tested it in an *in vitro* model of HCV infection; this protein corresponds to the therapeutic of the specification and the claims. As shown in Exhibit 2, the therapeutic protein, referred to as IB657, inhibits EMCV infection of hepatoma

(Huh7) cells.

10. On information and belief, the Office Action at page 10, lines 16-17, alleges that "the method of identifying a drug target based on genetic differences between two groups is not trivial and requires years to complete..." Although I agree that identifying a drug target is not "trivial," as it is in fact a major breakthrough, I strongly disagree that it takes years to complete. By following the methods described in this application, we identified a drug target (the mutated gene OAS1) initially in about six months and a drug in three years from start to preclinical drug candidate. A single cycle of data input, review and analysis according to the invention led directly to this drug discovery.

11. On information and belief, the Office Action at page 10, lines 14-15, alleges that "the identification of a drug target requires the sorting out of 1000's of targets present in most organisms." What applicants have disclosed and claimed is not the current method of target and drug discovery, but new methods. The drug currently undergoing preclinical testing, as described in paragraph 9 above, was developed at a fractional cost of the conventional approach. Furthermore, in addition to the cost benefit, the drug has entirely different toxicity parameters. The drug is based on studying ARU populations who already express a version of the drug and enjoy the beneficial effects of having it in their system. Therefore, the drug we developed is expected to have negligible toxicity compared to traditional drugs based on synthetic chemistry approaches. Thousands of targets were not "sorted out." The ARA and ARU comparison of the invention obviates that kind of historically laborious effort.

12. The drug that is the subject of paragraphs 9 and 10 above is one of many polypeptides disclosed and claimed in our subsequent co-pending patent application, Serial No. 10/972,135. The polypeptide of SEQ ID NO:48 has been found to be free of the art.

13. The 10/972,135 application was granted Special Status in a Decision on

Petition granted on December 7, 2005. The ground for the Petition was that applicant Illumigen is a Small Entity and the subject matter of the application is a major asset of the company. The Small Entity status of the company and the granting of the Petition to Make Special in the co-pending application are further evidence that the present patent application is fully enabling, because the target and the drug were discovered in less than three years through the work of far fewer employees, and using far fewer resources and expenses, as compared to drug discovery at a traditional pharmaceutical company.

I further declare that all statements made herein of my own knowledge are true and that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code.

Shawn Iadonato, Ph.D.

State of Washington)
) ss.
County of *King*)

On this 9th day of February, 2006, before me, a Notary Public in and for the State and County aforesaid, personally appeared Shawn Iadonato, Ph.D. to me known and known to me to be the person of that name, who signed and sealed the foregoing instrument, and he acknowledged the same to be his free act and deed.

TERRI RAY NOTARY PUBLIC COMMISSION EXPIRES 10-29-08 STATE OF WASHINGTON

Notary Public Terri Ray

Commission expires 10/29/08

SEA 1943722v1 0055382-000003

EXPRESS MAIL NO.

PATENT

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Alexandria, VA 22313-1450

Affidavit of Richard M. Myers, Ph.D. under 37 C.F.R. § 1.132

I, Richard M. Myers, Ph.D. being duly sworn, say:

1. I am an internationally recognized scientist and I am employed as Chairman of the Department of Genetics, Stanford University School of Medicine. I also hold positions as Stanford W. Ascherman Professor of Genetics, and Director, Stanford Human Genome Center, both in the Department of Genetics at Stanford University School of Medicine. I received a Bachelors Degree in Biochemistry in 1977 from the University of Alabama, and a Ph.D. degree in Biochemistry in 1982 from the University of California at Berkeley. I currently serve on the Scientific Advisory Board of Illumigen Biosciences, Inc.

2. I am an author or co-author of over 130 peer-reviewed research articles and I have been invited to give presentations on my research at national and international meetings. I was a founding scientist of Mercator Genetics, Inc., and an original member of the scientific advisory board of Genaissance Pharmaceuticals. I am the recipient of several awards related to my work in genetics and the human genome, including the Wills Foundation Award, 1986-2005; the Pritzker Foundation Award, in 2002; and the Searle Scholar Program, from 1987-1990. These and other awards, as well as the details of my publications, are listed in my curriculum vitae, which is attached as Exhibit 1.

3. On information and belief, claims of the present application have been rejected under 35 U.S.C. § 112, first paragraph. According to the Office Action dated June 16, 2006, claims 1-10, 14-26, 28, 31-44 and 46-55 fail to comply with the enablement requirement because allegedly there is "undue experimentation required to go from the classification results achieved by implementing the invention to drug target identification without some prior knowledge of a relationship between a potential target and a biological condition as claimed." It is my opinion that the methods described in the application taken together with the state of the art at the time of the application support the enablement of the claimed invention. As discussed below, I conclude that undue experimentation would not be required to identify a drug target using the methods of the invention.

4. On information and belief, the Office Action at page 6, lines 3-4, alleges that "there would be an unpredictable amount of experimentation required to practice the claimed invention." Inasmuch as the methods of the present invention relate to epidemiological, statistical, and genetics analyses, I disagree that the amount of "experimentation" is unpredictable. In fact, I disagree with use of the term experimentation as the much of the genetics work (that the examiner appears to believe not enabled in the application) is routine. In my work as a federally funded scientist, like others in my field, I am routinely required to predict the amount of effort required in my proposals to funding agencies. Additionally, over a nine year period, I was a standing

member of two National Institutes of Health sStudy Sections (and Chair of one of them) that review proposals from scientists representing a broad cross-section of skill in these arts. Following that, I was a member for four years of the Advisory Council—the group of experts that give the final sign-off for funding decisions to the Director—of the National Human Genome Research Institute (one of the NIH institutes). In my experience, it is routine for such proposals to make predictions with reasonable accuracy about the amount of effort required for studies similar to those required by the claimed invention.

5. On information and belief, the Office Action at page 10, lines 15-17, alleges that "the method of identifying a drug target based on genetic differences between two groups is not trivial and requires years to complete...." Although I agree that identifying a drug target is not "trivial," I disagree that it would require years to complete if the claimed methods are followed. Based on my scientific knowledge of molecular genetics and infectious disease, I am familiar with the methods routinely used to identify mutations in genes and to correlate these mutations with protein expression. My own research involves the study of the structure, function and evolution of the human genome, and I design and perform experiments to understand the role of genes in human diseases. In the course of my career spanning over two decades, I have worked closely with numerous scientists of varying levels of training and expertise, and I have collaborated with laboratories of several foreign countries. I also serve as Editor of the publication *Genome Research*, so I am familiar with the skill level of scientists in my areas of expertise. It is my opinion that anyone of ordinary skill in the field of molecular genetics would have a comparable level of familiarity and expertise.

6. I am aware that it is possible and routine to identify a mutation without knowledge of the underlying disease mechanism, and to determine whether that mutation corresponds to phenotypic characteristics of a subpopulation, such as the "at risk unaffected". For example, I work in the areas of brain and cardiovascular phenotypes as well as infectious diseases, and I study the role of genes in these and other diseases. In these areas and more, it is routine to identify genetic mutations

associated with phenotypic characteristics (e.g. inherited diseases) without previous knowledge of a relationship to the biological condition. In the context of the claim language and the patent specification, I understand that a population "at risk" could be a population exposed to an infectious agent, a subpopulation "at risk and affected" would be a population exhibiting a phenotypic trait, such as evidence of infection, and that a subpopulation "at risk and unaffected" would be a population expected to have the disease on the basis of history of exposure, yet not exhibiting phenotypic evidence of the infection (*i.e.* symptomatic, serum antibodies, *etc.*).

7. As a scientist working closely with physicians and epidemiologists to study the genetic basis of human disease, I am aware of the procedures and requirements for identifying matched individuals for conducting risk analysis of infections and other diseases. In my opinion, identifying "at risk unaffected" and "at risk affected" populations, and obtaining biological samples, such as blood samples, is routine and need not be time-consuming. Such samples are routinely obtained in the course of medical examination and diagnosis. Using well-known methods of sequence analysis and mutation identification, it is entirely feasible and within ordinary skill in this art to identify a genetic difference that correlates with the affected versus unaffected phenotype. Then, using the vast resources available in the gene databases, including sequences obtained as a result of the Human Genome Project, it would not require undue experimentation to identify a protein or regulatory region that correlates with the observed genetic difference. Indeed, I have either led or been actively involved in several studies that identified DNA sequence variants that are associated with human diseases, including an inherited form of childhood epilepsy, hemochromatosis, basal cell nevus syndrome (of which skin cancer is a symptom), and several others. I participated in the Human Genome Project from its inception, and my laboratory was funded to collaborate on the sequencing of human chromosomes 5, 16 and 19. As a result of this work, I am familiar with the use of the human genome sequences and their availability and utility to anyone of ordinary skill in this art.

8. On information and belief, the Office Action at page 7, lines 2-3, alleges that "the claims are broad in that they are drawn to identification of a drug target for any given biological condition." Based upon my experience and the prior art, it is my belief that the methods of the claimed invention are broadly applicable; certainly applicable beyond simply infectious disease.

9. On information and belief, the Office Action at page 8, line 18, alleges "a polypeptide is not a drug target" as a rationale for not accepting applicant's prior supportive arguments. I strongly disagree with this position and submit that entire classes of important drugs (e.g. monoamine oxidase inhibitors and angiotensin converting enzyme (ACE) inhibitors) act on polypeptide drug targets. In fact, most small molecule drugs are inhibitors of proteins, thus making the proteins themselves the drug targets. Furthermore, there are well-known polypeptide therapies (e.g. insulin and growth hormone) where a polypeptide is the drug itself.

10. On information and belief, the Office Action at page 10, lines 4-5, alleges that "the details for identifying a drug target based on the classification are not described. Thus, there is not sufficient support to enable one skilled in the art of make or use the invention." I strongly disagree with this statement for the following reasons. First, applicants do describe general methods to identify functional mutations differentially associated with the ARU and ARA groups. Second, association methods for identifying genetic mutations, such as those described by example in the application, have been well known in the art since the 1990s. Third, identification of such mutations by comparison with the "at risk unaffected" group that de facto identifies a target. This latter point is in contrast to the traditional analysis using only "at risk affected" groups for disease gene identification which does not generally identify a target.

11. It is an advantage of the present methods that no traditional biochemical screening is required. I am well-qualified to provide an opinion on the differences between traditional biochemistry-based screening, and the new methods disclosed and claimed in this patent application. Instead, screening is performed by computer by

comparing the polynucleotides from the "at risk affected" and "at risk unaffected" groups. One of ordinary skill will be familiar with the input of data from human samples and the methods and search parameters for identifying genetic differences between two samples. This genetic, information-based analysis is a far more efficient, fast, and cost-effective method of identifying the relevant biochemical difference or differences between at-risk populations with and without the disease. It is the comparison of the observed genetic difference (*e.g.* point mutation, deletion, insertion) with the database to pinpoint the modified region and identify the function that leads directly to identification of a target.

12. On information and belief, the Office Action at page 10, lines 14-15, alleges that "identification of a drug target requires the sorting out of 1000's of targets present in most organisms." Based upon my knowledge of genetics and my direct experience in the field over the course of the past two decades, this statement is incongruous with the history of biomedical research.

13. In conclusion, I am a person with knowledge of the ordinary skill in this art, and in my professional capacity I will be a consumer of the new methods provided by the patent application. It is within my ability to understand and follow the claimed methods. For any disease in which the phenotype is related to a genetic difference, I would expect the claimed methods to allow me to discover that difference, and to correlate it with a gene product, such as a protein. That gene product in turn will correlate with the phenotypic difference between "at risk unaffected" (ARU) and "at risk affected" (ARA) individuals. This information will allow me to identify a target around which a treatment could be designed to mimic the protective phenotype of the "at risk unaffected" individuals.

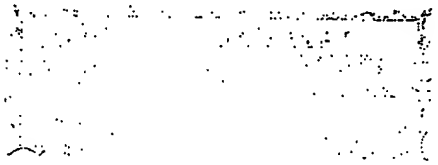
I further declare that all statements made herein of my own knowledge are true and that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code.

Richard M. Myers

Richard M. Myers, Ph.D.

State of California)
San Mateo) ss.
County of ~~Santa Clara~~

On this 16 day of December 2006, before me, a Notary Public in and for the State and County aforesaid, personally appeared Richard M. Myers, ~~Ph.D.~~, to me known and known to me to be the person of that name, who signed and sealed the foregoing instrument, and he acknowledged the same to be his free act and deed.



Notary Public

Commission expires Jan 13th, 2009

SEA 1856466v1 55382-3

EXPRESS MAIL NO.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Charles L. Magness and Shawn P. Iadonato
Application No.	:	09/707,576
Filed	:	November 6, 2000
For	:	SYSTEM AND METHOD FOR SELECTIVELY CLASSIFYING A POPULATION

Examiner	:	Anna Skibinsky
Art Unit	:	1631
Docket No.	:	55382-3
Date	:	December 15, 2006

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Affidavit of Cammie Lesser, M.D., Ph.D. under 37 C.F.R. § 1.132

I, Cammie Lesser, M.D., Ph.D. being duly sworn, say:

1. I am an internationally recognized scientist and I am employed as Assistant Professor at Massachusetts General Hospital/Harvard Medical School in Boston, Massachusetts. I received a Bachelors Degree in Biochemistry from Brown University, a Ph.D. degree in Biochemistry in 1993 from the University of California at San Francisco, and an M.D. degree in 1995 from the University of California at San Francisco.

2. I am an author or co-author of several peer-reviewed research articles and I have been invited to give presentations on my research at national and international

meetings. Prior to joining Massachusetts General Hospital/Harvard Medical School, I was a medical resident at the University of Washington. My curriculum vitae is attached as Exhibit 1.

3. On information and belief, claims of the present application have been rejected under 35 U.S.C. § 112, first paragraph. According to pages 9-10 of the Office Action dated June 16, 2006, claims 1-10, 14-26, 28, 31-44 and 46-55 fail to comply with the enablement requirement because allegedly there is "undue experimentation required to go from the classification results achieved by implementing the invention to drug target identification without some prior knowledge of a relationship between a potential target and a biological condition as claimed." It is my opinion that the methods described in the application support the enablement of the claimed invention. As discussed below, I conclude that undue experimentation would not be required to identify a drug target using the methods of the invention.

4. I am aware that it is possible and routine to identify a mutation without knowledge of the underlying disease mechanism, and to determine whether that mutation corresponds to phenotypic characteristics of a population such as the ARU group. In the context of the claim language and the patent specification, I understand that a population "at risk" could be a population exposed to an infectious agent, a subpopulation "at risk and affected" would be a population exhibiting a phenotypic trait, such as evidence of infection, and that a subpopulation "at risk and unaffected" would be a population expected to have the disease on the basis of history of exposure, yet not exhibiting phenotypic evidence of the infection (*i.e.* symptomatic, serum antibodies, *etc.*). I am also aware that the phenotypic definition of "at risk unaffected" varies from one biological condition to another and this definition allows the breadth of applicability of the present methods to conditions other than infectious disease.

5. As a medical doctor, I am aware of the procedures and requirements for identifying matched individuals for conducting risk analysis of infections and other diseases. In my opinion, identifying "at risk unaffected" and "at risk affected"

populations, and obtaining biological samples, such as blood samples, is routine and need not be time-consuming. Such samples are routinely obtained in the course of medical examination and diagnosis.

6. Based on my scientific knowledge of molecular genetics, I am familiar with the methods routinely used to identify mutations in genes and to correlate these mutations with functional effects, such as modification of protein amino acid sequence. I also appreciate how the identification of such functional genetic variations between ARA and ARU groups directly identifies the gene containing the genetic variations as a drug target. Anyone of ordinary skill in the field of molecular genetics would have a comparable level of familiarity and expertise.

7. On information and belief, the Office Action at page 8, lines 5-7, alleges that "applicants have not described how to identify where the genetic variation associated with the disease exists." The Office Action at page 8, line 21 through page 9, line 2, in a similar argument further alleges "it is not disclosed how the relevant polynucleotide is detected. Additionally, how the functional coding region carrying the genetic difference of interest is located." I disagree with these allegations. Applicants describe in the specification between page 10, line 22 and page 13 line 5, methods for detecting mutations and statistically associating those mutations with the ARA group relative to a control group. Using well-known methods of sequence analysis, mutation identification and statistical genetics, it is entirely feasible and within ordinary skill in this art to identify a genetic difference that correlates with the affected versus unaffected phenotype.

8. On information and belief, the Office Action at page 10, lines 14-15, alleges that "identification of a drug target requires the sorting out of 1000's of targets present in most organisms." I disagree with this statement. It is highly unlikely that few, if any, drug targets have been identified by "sorting out 1000's of targets present in most organisms."

9 On information and belief, what applicants have disclosed and claimed is not the traditional method of target and drug discovery. In fact, an advantage of the present methods is that they are the opposite of traditional methods. The present methods allow identification of a drug target by comparison of the ARA and ARU groups rather than by traditional approaches to drug target discovery. Many of the risk analyses and genetic comparisons outlined by the present methods are also amenable to computer automation. Thus the present methods provide a very effective short-cut to drug target discovery, and allow a researcher to identify relevant differences between the ARA and ARU subjects. The identification of the observed genetic difference (*e.g.* point mutation, deletion, insertion) between the "at risk unaffected" and "at risk affected" groups leads directly to identification of a target. The effect of the observed genetic difference on target function also leads the researcher to the type of required therapeutic intervention (e.g. protein replacement therapy versus antagonistic small molecule).

10. Because the target is identified in humans, the method of the invention provides at least two other differences from and advantages over traditional drug target identification. First, it circumvents much of the laboratory animal experimentation otherwise performed to identify a target. Second, because the at risk unaffected population is healthy, the method teaches development of a treatment that mimics the effect of the protective mutation in the ARU population. As such, a treatment that mimics the mutation is less likely to have the side effects that so often derail an otherwise promising drug treatment, sometimes when clinical trials are very advanced.

11. In conclusion, I am a person of ordinary skill in this art. It is within my ability to understand and follow the claimed methods. For any disease in which the phenotype is related to a genetic difference, I would expect the claimed methods to allow someone of my skill level to discover that difference, and to correlate it with a gene-specific effect, such as a protein modification. That gene–specific effect in turn will correlate with the phenotypic difference between "at risk unaffected" (ARU) and "at risk affected" (ARA) individuals. This information will allow one skilled in the art to

design a treatment to mimic the protective phenotype of the "at risk unaffected" individuals.

I further declare that all statements made herein of my own knowledge are true and that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code.

Cammie Lesser, M.D., Ph.D.

Commonwealth of Massachusetts)
) ss.
County of Middlesex)

On this 15 day of December, 2006, before me, a Notary Public in and for the Commonwealth and County aforesaid, personally appeared Cammie Lesser, M.D., Ph.D., to me known and known to me to be the person of that name, who signed and sealed the foregoing instrument, and she acknowledged the same to be her free act and deed.

Notary Public

Commission expires 1/19/2012

STACY B. SARNO, ESQ.
Notary Public
COMMONWEALTH OF MASSACHUSETTS
My Commission Expires January 19, 2012

Cubist Pharmaceuticals Acquires Illumigen Biosciences

Expects to File IND for Lead HCV Compound IB657 in 2008

LEXINGTON, Mass. & SEATTLE -- Cubist Pharmaceuticals, Inc. (NASDAQ: CBST) and Illumigen Biosciences, Inc. announced today that Cubist has acquired Illumigen pursuant to a definitive agreement and plan of merger entered into on December 24, 2007. Illumigen's lead compound is IB657, a protein therapeutic in pre-clinical development for the treatment of Hepatitis C Virus (HCV) infections. Cubist expects that an IND for IB657 will be filed in 2008.

Pursuant to the terms of the agreement, which was approved by the Boards of Directors of each company, Cubist will pay to the Illumigen stockholders $9 Million (after adjusting for Illumigen's closing cash balance) in cash and Illumigen has become a wholly-owned subsidiary of Cubist. Cubist will make payments during the development of IB657 as a therapy for HCV infections of up to $75.5 Million upon achieving certain development and regulatory milestones. If Cubist develops Illumigen products for the treatment of viruses other than HCV, development and regulatory milestone payments of up to $117 Million could apply. Assuming that HCV or other Illumigen antiviral products are commercialized, additional milestone payments of up to $140 Million, as well as tiered royalties, could apply.

Mike Bonney, President and CEO of Cubist Pharmaceuticals, said "We are excited about the opportunity of filing an IND for IB657 in the coming year and advancing it into the clinic. An HCV product candidate is an important addition to our pipeline, and leverages our antiinfective development, regulatory, and commercialization expertise."

Donald Elmer, Chairman of Illumigen Biosciences, said "We believe that Cubist is ideally positioned to exploit the immediate opportunity for IB657 against HCV, and potentially for additional viral infections."

No financing will be necessary to complete the acquisition of Illumigen or to fund the development of IB657. The impact of any charges related to purchase accounting, including in-process R&D, will be recorded in Cubist's 2007 full-year results.

About HCV

HCV is a virus that primarily targets the liver, currently causing infection in more than 4 million people in the U.S. and 180 million people worldwide. The virus is difficult to eradicate, with infected patients eventually developing chronic liver infection, and, in some cases, liver cancer. HCV infection is the most common reason for liver transplantation in the U.S. and Western Europe and the leading cause of death from liver disease.

No vaccine is currently available to prevent HCV infection. Current HCV therapy combines a pegylated-interferon with ribavirin for up to 48 weeks of treatment. Current therapy has significant problems with both safety (e.g., significant treatment limiting adverse effects and contraindications) and efficacy (e.g., 80% of HCV infections in the U.S. are due to genotype 1 virus for which the efficacy rate of current therapy is approximately 40 to 50%). The HCV market was $2.2 Billion in 2005 and is projected to double to $4.4 Billion in 2010. This growth will be driven by an increase in the number of patients being treated, uptake of new drugs, and the use of multi-drug treatment regimens.

About IB657

IB657 is a pre-clinical protein therapeutic being developed for treatment of HCV infection. Based on its antiviral activity, IB657

may have therapeutic utility in the treatment of certain other viral diseases. Pre-clinical studies to assess activity against these viruses may occur in parallel with its development for HCV infection.

About Illumigen

Illumigen Biosciences, Inc. was co-founded by Drs. Charles Magness and Shawn Iadonato in 2000 to discover beneficial human genetic mutations that might provide a roadmap for novel therapeutic drug mechanisms. The discovery of IB657 resulted from an investigation into the cause of apparent immunity to HCV infection enjoyed by people with a specific naturally occurring genetic mutation. Prior to founding Illumigen, Drs. Magness and Iadonato both were involved in the Human Genome Project. Illumigen is a Seattle-based, privately held biopharmaceutical company financed by Pacific Horizon Ventures in Seattle, WA. Additional information can be found at Illumigen's web site at www.illumigen.com and www.pacifichorizon.com.

About Cubist

Cubist Pharmaceuticals, Inc. is a biopharmaceutical company focused on the research, development, and commercialization of pharmaceutical products that address unmet medical needs in the acute care environment. In the U.S., Cubist markets CUBICIN[R](daptomycin for injection), the first antibiotic in a new class of anti-infectives called lipopeptides. The Cubist product pipeline includes pre-clinical programs that address unmet medical need in Gram-positive infections, Gram-negative infections, and CDAD (Clostridium difficile-associated diarrhea). Cubist is headquartered in Lexington, MA. Additional information can be found at Cubist's web site at www.cubist.com.

Cubist Safe Harbor Statement

Statements contained herein that are not historical fact may be forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934, and such statements are subject to a variety of risks and uncertainties. There are a number of important factors that could cause actual results to differ materially from those projected or suggested in any forward-looking statements made by Cubist. These factors include, but are not limited to: (i) the level of acceptance of CUBICIN by physicians, patients, third-party payors and the medical community; (ii) any changes in the current or anticipated market demand or medical need for CUBICIN; (iii) any unexpected adverse events related to CUBICIN, particularly as CUBICIN is used in the treatment of a growing number of patients around the world; (iv) competition in the markets in which we and our partners market CUBICIN, including marketing approvals for new products that will be competitive with CUBICIN; (v) whether the U.S. Food and Drug Administration, or FDA, accepts proposed clinical trial protocols that may be achieved in a timely manner for additional studies of CUBICIN or any other drug candidate we seek to enter into clinical trials; (vi) whether we will receive, and the potential timing of, regulatory approvals or clearances to market CUBICIN in countries where it is not yet approved; (vii) legislative and policy changes in the United States and other jurisdictions where our products are sold that may affect the ease of getting a new product or a new indication approved; (viii) changes in government reimbursement for our or our competitors' products; (ix) whether or not third parties may seek to market generic versions of our products by filing Abbreviated New Drug Applications, or ANDAs, with the FDA, and the results of any litigation that we file to defend and/or assert our patents against such generic companies; (x) our ability to conduct successful clinical trials in a timely manner; (xi) the effect that the results of ongoing or future clinical trials of CUBICIN may have on its acceptance in the medical community; (xii) the ability of our third party manufacturers, including our single source provider of active pharmaceutical ingredient, or API, to manufacture sufficient quantities of CUBICIN in accordance with Good Manufacturing Practices and other requirements of the regulatory approvals for CUBICIN and at an acceptable cost; (xiii) our dependence upon collaborations with our partners and our partners' ability to execute on development, regulatory and sales expectations in their territories; (xiv) our ability to finance our operations; (xv) the effectiveness of our sales force and our sales force's ability to access targeted physicians; (xvi) potential costs resulting from product liability or other third

party claims; (xvii) our ability to protect our proprietary technologies; (xviii) our ability to consummate the transaction with Illumigen, (xix) our ability to develop and commercialize products based on IB657, (xx) the market for HCV products and the demand for products based on IB657; (xxi) our ability to integrate successfully the operations of Illumigen or any other business that we may acquire and the potential impact of the acquisition of Illumigen or any other future acquisition on our financial results; (xxii) our ability to discover, acquire or in-license drug candidates and develop and achieve commercial success for drug candidates; and (xxiii) a variety of risks common to our industry, including ongoing regulatory review, public and investment community perception of the industry, legislative or regulatory changes, and our ability to attract and retain talented employees.

Additional factors that could cause actual results to differ materially from those projected or suggested in any forward-looking statements are contained in Cubist's recent filings with the Securities and Exchange Commission, including those factors discussed under the caption "Risk Factors" in such filings.

Cubist and CUBICIN are registered trademarks of Cubist Pharmaceuticals, Inc.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Charles L. Magness
Application No.	: 09/707,576
Filed	: November 6, 2000
For	: System and Method for Selectively Classifying a Population
Examiner	: Anna Skibinsky
Art Unit	: 1631
Docket No.	: 55382-3
Date	: August 13, 2008

Attention: Board of Patent Appeals and Interferences
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPELLANT'S BRIEF (37 C.F.R. § 41.37)

Commissioner for Patents:

Appellants appeal from the final rejection of claims 1-10, 14-26, 28, 32-44 and 46-55 of the above-identified application. This Brief on Appeal is submitted in response to the Office Action of May 16, 2007, rejecting the claims, and the Advisory Action of December 20, 2007, declining to enter the amendment of November 16, 2007. The appeal is proper because the claims have been rejected twice.

The fees required under Section 1.17(c) are dealt with in the accompanying transmittal letter.

I. REAL PARTY IN INTEREST

The real party in interest in the above-identified application is Illumigen, Inc., which has its principal place of business at c/o Cubist Pharmaceuticals, Inc., 65 Hayden Avenue, Lexington, MA 02421.

II. RELATED APPEAL AND INTERFERENCES

No other appeals or interferences will directly affect, be affected by, or have a bearing on the Board of Patent Appeals and Interferences' decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 11-13, 27, 29-31, and 45 were previously cancelled. Claims 56-61 are withdrawn from consideration. Claims 1-10, 14-26, 28, 32-44 and 46-55 stand rejected and are the claims on appeal. No other claims are pending.

IV. STATUS OF AMENDMENTS

In a response filed on November 16, 2007, appellants sought to cancel claims 1-10, 14-19, 47, 49, 50 and 51 to narrow the issues, but the Examiner declined to enter that amendment, as indicated in the Advisory Action dated December 20, 2007. In the response, appellants also amended claims 20-23 and 25, but that amendment was not entered. The claims as shown in the accompanying Appendix are an accurate representation of the pending claims.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 provides a computer-implemented method for identifying a drug target associated with a selected biological condition, and is described in the specification at page 14 line 20 to page 17 line 20 and in Figures 1 and 2.

Dependent claim 2 specifies the generation of statistical data that are analyzed for classifying the population, and is described at page 3, lines 22-27.

Dependent claims 3-10 further define the classification of populations and statistical analyses, and are described at page 3, line 28 to page 4, line 9.

Dependent claims 14-19 further define the populations being analyzed as ARA, ARU, and URU. These are defined at page 3, lines 22-27; page 6, lines 5-16; page 19, lines 10-17; and page 30, lines 10-23.

Appellants previously sought to cancel claims 1-10 and 14-19. Independent claim 20 provides a computer-implemented method of data analysis for identifying a

target for use in treating a selected biological condition. Claim 20 is described at page 14, line 20 to page 17, line 20 and Figures 1 and 2.

Dependent claims 21-26 define aspects of the method in terms of how the disease characteristics, risk characteristics, and status are categorized to identify a target, and are supported at page 5, line 24 to page 6, line 4.

Dependent claim 28 provides that the medical histories of the subjects are compared with the medical test results of the groups. The claim is supported at page 30, lines 24-28.

Dependent claims 31-40 further define how targets are identified, how subjects are classified, and what test results are used. The claims are supported at page 32, line 13 to page 34, line 16.

Independent claim 41 provides a system for data analysis to identify a target for treating a selected biological condition, as supported at page 14, lines 20-28 and Figure 1. Dependent claims 42-46 further define actions of the processor of claim 41 in relation to numerical scores and data, as supported at page 6, lines 17-26; page 19, lines 10-17, and page 30, lines 10-23.

Dependent claims 47-51 depend from claim 1 or 20, and provide specific embodiments of the method in relation to identifying a target. Claim 47 provides identifying a drug target (page 13, lines 16-20). Claim 48 provides identifying a diagnostic assay (page 34, lines 11-16). Claim 49 provides identifying a vaccine (page 34, lines 11-16). Claims 50 and 51 provide identifying a candidate drug (page 5, lines 14-18).

Claims 52-55 depend from claim 41, and provide for identifying a drug target, a candidate drug, a diagnostic assay, and a vaccine. (Page 34, lines 10-18; page 34, lines 11-16.)

Appellants previously sought to cancel claims 29-61.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Did the Examiner err by failing to withdraw the finality of the Office Action dated May 16, 2007 when that Action did not comply with the M.P.E.P. section governing final rejection language?

II. Did the Examiner err by rejecting claims 1-19, 47, 49, 50 and 51 for allegedly being directed to non-statutory subject matter, when appellants previously amended these claims as suggested by the Examiner, to address the Examiner's ground of rejection?

III. Did the Examiner err by rejecting claims 1-10, 14-26, 28, 31-44, and 46-55 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement, because the claims as amended are enabled, as attested to by three experts?

VII. ARGUMENTS

Introduction

Prosecution of this application has now lasted almost eight years since it was filed on November 6, 2000. The application has been transferred between Examiners, causing progress made with one Examiner to be lost when the next Examiner effectively started over. Several personal interviews have been held, and many rounds of Office Action and Amendment are of record. Affidavits of experts have been carefully prepared and filed. The history is summarized below.

The application had been pending for three years when the undersigned conducted a personal interview with Examiner C. Michelle Colon and Supervisory Examiner Tariq Hafiz. The interview was intended to serve as an overview of the invention, and to establish communication going forward.

A first action was mailed on June 16, 2004, and raised issues under 35 U.S.C. §§ 101, 102(e), and 103. There were no § 112 rejections. On August 26, 2004, appellants conducted a telephonic interview with Examiner Colon. The Examiner suggested amendment to the claims to clarify claim language. Appellants filed a response on September 13, 2004. The claims were amended as discussed with the Examiner, and arguments were made to address the prior art rejections.

A second and final Office Action was mailed on January 3, 2005. The 35 U.S.C. § 101 rejection was withdrawn in view of the claim amendments, and the prior art rejections were withdrawn. A new rejection under 35 U.S.C. § 102(a) was asserted

over five "risk assessment" articles published by the NIH, despite the action being final. The previous prior art rejections under §§ 102(e) and 103 were not retained.

On March 28, 2005, appellants further amended the claims to address an informality, and argued that the claims were not anticipated by the NIH references cited under 35 U.S.C. § 102(a).

On April 8, 2005, the Examiner issued an Advisory Action stating that the proposed amendment raised new issues requiring further search and consideration.

Appellants filed a request for continuing application, and the amendment filed on May 2, 2005 was entered. The case had been transferred to Examiner Anne Skibinsky and Supervising Examiner Ardin Marschel. An Office Action was mailed on August 29, 2005. The Examiner stated that claims 1-10, 14-26, 28, 31-44 and 46-55 (all the pending claims) contained new matter, and rejected them under 35 U.S.C. § 112, written description and enablement. The rejection of claims 1-10, 14-26, 28, 31-44, and 46-55 under 35 U.S.C. § 102(a) over the NIH publication was maintained.

A response was filed on February 24, 2006. Appellants amended the claims to address individually each of the Examiner's points about claim language. Table 1 at pages 19-21 of the amendment provides precise support in the specification for each term that the Examiner questioned.

Appellants addressed the enablement rejection by discussing the *Wands* factors. *In re Wands*, 8 U.S.P.Q. 2d 1400, 1404 (Fed Cir. 1988). In support of particular factors, appellants submitted an Affidavit of an expert. Dr. Shawn Iadonato's affidavit attested to the amount of direction or guidance provided. According to Dr. Iadonato, when the guidance in the specification was followed, a target and drug for treating hepatitis C were identified. This affidavit also contested the Examiner's statement that the discovery of one drug target costs hundreds of millions of dollars and several years of research time.

Regarding the rejection under 35 U.S.C. § 102(a) (NIH publication), appellants explained in detail how the claim language distinguished the inventive methods from the cited art methods.

In an Office Action dated June 16, 2006, the Examiner withdrew new claims 56-61 from consideration. Regarding the grounds of rejection, the affidavit of Dr. Shawn

Iadonato was deemed insufficient to overcome the enablement rejection because (a) Dr. Iadonato was said to be of extraordinary skill in the art; (b) the affidavit did not establish when the experiments were performed; (c) a URU population wasn't mentioned in the independent claims; and (d) the affidavit only supported identification of a drug target for hepatitis C.

Claims 1-19, 47, 49, 50 and 51 were rejected under 35 U.S.C. § 101 as the claims allegedly were directed to non-statutory subject matter. At the sentence bridging pages 4-5, the Examiner seemed to offer a remedy:

> An example which would make the instant method steps statutory would be to include a step of displaying the data for a user. Hence, the data would become concrete, tangible, and useful. (Emphasis added.)

Claims 1-10, 14-26, 28, 31-44, and 46-55 were rejected under 35 U.S.C. § 112, first paragraph, enablement.

The following rejections were withdrawn:

a. Rejection under 35 U.S.C. § 112, second paragraph, vague and indefinite.

b. Rejection under 35 U.S.C. § 102 over the NIH risk assessment models.

At this stage, appellants had narrowed the issues to rejections for (a) lack of utility (for which the Examiner had offered remedial language) and (b) lack of enablement. The next amendment was prepared for addressing these remaining issues, and it was filed on December 18, 2006.

Appellants amended claim 1 to recite a step of displaying the data for a user – language suggested by the Examiner. Support in the specification was indicated.

In response to the enablement rejection – the only other remaining rejection – appellants submitted three affidavits of experts. Appellants addressed each of the Examiner's comments individually and thoroughly. The experts are discussed below.

Expert 1, Dr. Cammie Lesser. Dr. Cammie Lesser is an internationally recognized scientist and physician employed as Assistant Professor at Massachusetts General Hospital/Harvard Medical School in Cambridge, Massachusetts. She received a Bachelors Degree in Biochemistry from Brown University, a Ph.D. degree in Biochemistry in 1993 from the University of California at San Francisco, and an M.D. degree in 1995 from the University of California at San Francisco. She is an author or

co-author of several peer-reviewed research articles and has been invited to give presentations on her research at national and international meetings. Prior to joining Massachusetts General Hospital/Harvard Medical School, she was a medical resident at the University of Washington.

Expert Dr. Cammie Lesser attested that the application provides a "very effective short-cut to drug target discovery." She also attested that the methods in the application are distinguished from current methods of target and drug discovery. She stated that she understood the meanings and implications of the terms employed, including the "at risk unaffected" (ARU) group. In paragraph 5, she concluded that as a medical doctor, she found it to be routine to identify "at risk unaffected" and "at risk affected" populations, and to obtain biological samples from these populations. At paragraphs 7-11, she refutes specific statements of the Examiner in concluding that she finds the application to be enabling for the claims.

Expert 2, Dr. Richard Myers. Dr. Richard Myers is an internationally recognized scientist employed as Chairman of the Department of Genetics, Stanford University School of Medicine. He also holds positions as Stanford W. Ascherman Professor of Genetics, and Director, Stanford Human Genome Center, both in the Department of Genetics at Stanford University School of Medicine.

He received a Bachelors Degree in Biochemistry in 1977 from the University of Alabama, and a Ph.D. degree in Biochemistry in 1982 from the University of California at Berkeley. In addition to authoring or co-authoring over 130 peer-reviewed research articles, Dr. Myers has received awards relating to his work in genetics and the human genome, including the Wills Foundation Award, 1986-2005; the Pritzker Foundation Award, in 2002, and the Searle Scholar Program, from 1987-1990. Dr. Myers disclosed in his affidavit that he served on the Scientific Advisory Board of Illumigen Biosciences, Inc. at the time of signing the affidavit.

Expert Dr. Richard Myers attested to several factors that demonstrate enablement of the claimed invention. With his expertise in genetics, he stated that much of the genetics work that the Examiner deemed non-enabled was routine (Myers affidavit, paragraph 4.) He also stated that if the claimed methods were followed, it would not require years to complete the identification of a drug target. (Paragraph 5.)

He further stated that it is possible and routine to identify a mutation without knowledge of the underlying disease mechanism. (Paragraph 6.) In paragraphs 8-12, he specifically addressed and refuted individual statements of the Examiner that related to the alleged lack of enablement.

Expert 3, Dr. Shawn Iadonato. Appellants submitted a new affidavit of Dr. Shawn Iadonato, who is also a co-inventor. Dr. Iadonato received a Bachelors Degree in Biology from the University of Pennsylvania in Philadelphia and a Ph.D. degree in Genetics from the University of Washington. He is an author or co-author of numerous peer-reviewed research articles and has been invited to give numerous presentations on his research at national and international meetings.

Dr. Iadonato managed sequence data collection for the University of Washington Genome Center. He subsequently served as Founder, Vice-President, and Chief Scientific Officer of Illumigen Biosciences, Inc., the applicant and assignee of the present patent application. In that capacity, he managed the scientific and drug development programs of Illumigen. He has more than ten years experience developing and managing large-scale genetics and genomics projects, most notably involving his work on the Human Genome Project.

The Examiner had deemed Dr. Iadonato to be of "extraordinary" skill. In recognition of the Examiner's position on this, Dr. Iadonato's new affidavit was careful to focus on enablement issues he was uniquely qualified to evaluate. He stated that the first time the claimed methods were followed, they led to discovery of a mutation that correlated with resistance to hepatitis C.

At this stage, appellants had made a thorough and *bona fide* attempt to alleviate all the Examiner's remaining concerns, including adding claim language suggested by the Examiner.

It was therefore a surprise to receive the Office Action dated May 16, 2007 wherein the Examiner maintained the rejection under 35 U.S.C. § 101. The Examiner also maintained the rejection under 35 U.S.C. § 112, first paragraph, enablement, despite the careful and thoughtful affidavits, to which the experts devoted substantial personal time and effort.

The Examiner cited numerous reasons why she found the expert affidavits to be unpersuasive. The Examiner focused on very specific wording in the affidavits and found that that precise wording was not mirrored in the claims. Appellants submit that experts expressed complex scientific concepts in their own words, and it is important to look at the meaning, not to focus on minor variations in language.

The Examiner also substituted her opinion for the experts' statements. As one example, at page 18, lines 5-6, regarding the affidavit of Dr. Myers, she states, "[d]etermining which of these is a 'drug target' requires undue experimentation as one skilled in the art would have to guess at which is truly causative of disease symptoms, and would have to perform further research to confirm that guess." This completely disregards the expert opinion of a scientist who makes his living evaluating how much experimentation would be needed to conduct a successful research project. The Examiner addresses that incongruity by stating that Dr. Myers' extensive experience in evaluating grant proposals is not equivalent to predicting success of a research project, then she extends that to dismissing Dr. Myers' ability to evaluate enablement of a claimed invention. (Page 16, lines 6-10.)

Regarding the affidavit of Cammie Lesser, M.D., Ph.D., the Examiner chooses to disagree with Dr. Lesser's expert opinion on what experimentation is routine. See page 22, lines 4-5 of the Office Action, "[t]he Examiner maintains that this is not routine and represents undue experimentation." Appellants submit that it is not the Examiner's role to substitute her opinion for that of Dr. Lesser.

Regarding the affidavit of Dr. Iadonato, the Examiner seems to acknowledge that a drug was in fact identified in short time using the claimed methods (Office Action, page 24, lines 14-16); she nevertheless finds fault with the affidavit because Dr. Iadonato does not use language that is identical to the claim language. For example, see page 24, lines 7-11: by stating "studying ARU populations who already express a version of the drug," Dr. Iadonato was using language intended to be readily understood, yet equivalent to the claim language cited by the Examiner, "identification of a drug target based on genetic variations between broadly defined populations."

The fact of the discovery of a promising treatment for hepatitis C using the claimed methods has been dismissed by the Examiner as not supportive of enablement.

Appellants submit that reduction of the claimed method to actual practice, and high valuation of the resulting product by the pharmaceutical industry, are strong indicia that the claims are in fact enabled as attested to by highly qualified experts.

The Examiner also made the action final but failed to include the "final action" language as provided by the M.P.E.P. This is discussed in Argument I herein.

Appellants at that stage were highly motivated to move the application forward. In a response filed on November 16, 2007, they canceled claims 1-12, 14-19, 31-44, and 46-61. This rendered moot the rejection under 35 U.S.C. § 101, and clearly signaled appellants' desire to resolve the issues without further prolonged prosecution. At this point, the case had been pending for seven years.

Appellants further amended the claims to address the remaining issues. Only eight claims remained: claims 20-26 and 28. However, instead of working with appellants to resolve the issues for this significantly reduced claim set, the Examiner neither withdrew the finality as requested, nor did she consider the short amendment, which only had five pages of remarks.

On December 20, 2007, an Advisory Action was mailed. The amendments to the claims were deemed to introduce a substantive change requiring further search and consideration.

Appellants filed a Request for a Pre-Appeal Brief Review, and in a Notice mailed on May 6, 2008, the Panel stated that the case was in condition to proceed to the Board of Patent Appeals and Interferences. This appeal therefore follows.

While this application has been pending, the disclosed invention has led a successful life, both scientific and commercial, in the laboratory and in industry, and the first product of the inventive method is heading for the clinic. The original assignee, Illumigen Biosciences Inc., was acquired by Cubist Pharmaceuticals, Inc., on December 24, 2007, in part on the strength of the drug target whose discovery is discussed in the expert affidavits that the Examiner found to be unpersuasive. An IND for the lead compound is expected to be filed in 2008.

That compound, a polypeptide, was identified by appellants as a variant protein produced by ARU populations who were resistant to hepatitis C infection despite repeated exposure. The *phenotype* of these ARU populations differ from the phenotype

of the matched ARA populations (exposed to hepatitis C and infected), and the differing *genotypes* is manifested by production of the variant protein that itself is the therapeutic agent. This represents a real-life embodiment of the claims. A copy of the press release is submitted herein as Exhibit 5. (It was not previously of record because the acquisition of Illumigen Biosciences, Inc. took place after appellants filed the most recent amendment, on November 16, 2007.)

This Brief on Appeal is filed to seek the Board's position on the prosecution and to direct the case to allowance, or to clarification of the issues so that appellants can address those issues in a manner that moves the case forward, not backward.

I. Did the Examiner err by failing to withdraw the finality of the Office Action dated May 16, 2007? Although the box was checked indicating that the May 16, 2007 Office Action was final, that Office Action failed to include the proper paragraph as provided for in M.P.E.P.:

> 7.39 Action is Final
>
> THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy set forth in 37 CFR 1.136(a).
>
> A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Because the paragraph was not included in the May 16, 2007 Office Action, appellants were not given the notice regarding deadlines, and the simple checking of a box could have been a clerical error, not the Examiner's decision.

Appellants urged that the Examiner withdraw the finality. This was especially requested under the circumstances of the November 16, 2007 amendment cancelling most of the claims and significantly narrowing the issues which the Examiner had to

consider prior to issuing the next communication, which appellants submit should not have been an Advisory Action refusing to enter an amendment that clearly was positioning the case for allowance or at least for negotiation with the Examiner on any remaining points of claim language.

Appellants therefore argue that the finality should be withdrawn and the November 16, 2007 amendment be entered.

Appellants attempted to cancel claims 1-10, 14-19, 47, 49, 50, and 51 in the amendment filed November 16, 2007. Since the Examiner refused to enter the amendments, the claims remain pending. Cancelling claims 1-10, 14-19, 47, 49, 50, and 51 would have rendered moot the rejection under 35 U.S.C. § 101.

II. Did the Examiner err by rejecting claims 1-19, 47, 49, 50 and 51 under 35 U.S.C. § 101?

With regard to the claim rejections under 35 U.S.C. § 101, appellants respectfully submit that in the Office Action dated June 16, 2006, the Examiner suggested that this rejection could be overcome by, "includ[ing] a step of displaying the data for a user. Hence, the data would become concrete, tangible, and useful." See page 5, Office Action dated June 16, 2006.

Claim 1 was amended to read as follows(the entire claim is found in the Claims Appendix) :

> 1. (Currently Amended) A computer-implemented method for the identification of a drug target associated with a selected biological condition, comprising:
>
> [lines omitted for brevity]
>
> performing a computer analysis of genetic data from the ARA sub-population and the ARU sub-population to identify genetic variations therebetween;
>
> and displaying each of the identified target candidate genes to a user...

The support for the amendment to recite displaying identified target candidate genes to a user is found throughout the description of Figure 1 at page 15, line 3 to page 16, line 8, as well as page 17, lines 1-3.

Despite appellants' amendment to the claims reciting a step of displaying the data for a user in the response to the June 16, 2006 Office Action, this rejection has been maintained. See pages 3 and 16, response dated December 18, 2006, and in the May 16, 2007 Office Action. Thus, appellants respectfully submit that this rejection should be withdrawn.

III. Did the Examiner err by rejecting claims 1-10, 14-26, 28, 31-44 and 46-55 under 35 U.S.C. § 112, first paragraph? Appellants respectfully submit that the Examiner has failed to adequately consider the originally filed application as well as the expert affidavits previously filed. Appellants submit that no undue experimentation is required to practice the presently pending claims. Affidavits by Drs. Lesser and Myers in support of the claims are of record. See pages 17-26 (and corresponding affidavits) of the amendment filed December 18, 2006. An affidavit of Dr. Iadonato, filed with a Supplemental Response dated February 22, 2007, was of record.

Appellants submit that each point of the Examiner's rejections had been addressed in previous responses. The claims relate to a computer-implemented method for identification of a drug target associated with a selected biological condition, comprising: using a computer to analyze stored data related to medical histories of a population; using a computer to analyze stored data related to medical test results for the population; and based on computer analysis of the data related to the medical histories and the data related to the medical test results, classifying the population into at least two phenotypic sub-populations.

These sub-populations are defined as at risk and affected (ARA), whose members have ever been affected by the selected biological condition, and at risk and unaffected (ARU), whose members ought to be affected by the selected biological condition at the present time based on a risk analysis, but are unaffected by the selected biological condition at the present time. The steps further include: performing a computer analysis of genetic data from the ARA sub-population and the ARU sub-population to identify genetic variations therebetween; displaying the data for a user; and using data related to the identified genetic variations between the ARA sub-population and the ARU sub-population to identify the drug target associated with the selected biological condition.

An element of the present invention is that prior knowledge of the genetic basis of a disease is not required for identification of a drug target. As set forth at line 22, page 10 – line 25, page 11 of the originally filed application, population members may be classified according to phenotype, and further characterized by genotype. In prior art techniques, the disease itself is studied by analyzing the defective genes and proteins of people afflicted with the disease or condition. In the present disclosure, by contrast, drug targets are identified through the use of ARU (at risk, unaffected) populations to discover the phenotype of people who are naturally resistant to the disease or condition. The differences that are found in the unaffected population become the basis of the treatment for that disease.

Figures 3-5 of the originally filed application illustrate the methods for defining the epidemiological ARA and ARU populations, as well as testing the sub-populations. A candidate drug target (whether a small molecule, polynucleotide, polypeptide, antibody, or other biological or chemical target) is determined based on the identification of the genetic differences in the phenotypically defined populations and/or sub-populations. In most cases, the target is easily discernible, for example, the case where a genetic difference causes one at-risk group of individuals to be unaffected but another at-risk group of individuals is affected.

For such a case, the person of skill in the art need only to identify the biological manifestation of the genetic difference, whether it is an increase, a decrease, or a change in the protein encoded by or regulated by the identified mutations. Without regard to the outcome of this last step, as soon as the target has been identified by the presence of mutations that associate with the ARU versus the ARA group, then the presently pending claims have been achieved. See for example, page 17, line 21, page 21, line 13, page 25, line 18, and page 30, line 8, of the originally filed application.

Expert affidavits were filed in support of appellants' statements. The Examiner did not afford the expert affidavits "meaningful consideration," as required under *In re Sullivan*, 498 F.3d 1345, 1356 (Fed. Cir. 2007). In *Sullivan*, the court stated that the declarations supported the applicants' arguments, and had the Board considered or reviewed the submitted declarations in any meaningful way, it might have come to a

different conclusion than it otherwise had. *Id.* Thus, when a patent applicant puts forth rebuttable evidence, the Board must consider that evidence.

Appellants respectfully submit that the Affidavits attest that use of the presently pending claims does result in identification of candidate drug targets, as exemplified by the identification of drug targets related to hepatitis C. In fact, candidate drug targets identified by the presently pending claims have resulted in discovery of a therapeutic polypeptide as an anti-viral therapy for hepatitis C. This therapeutic polypeptide is moving towards clinical trial. Thus, the testimony presented in the Affidavits confirms that the presently pending claims are fully enabled by the instant application.

Appellants submit that the claim amendments intended to overcome the § 112, first paragraph rejection were improperly refused entry, as a new search would not have been necessary if the amendment filed on November 16, 2007, were entered. The amendment focused the claims on one specific category ("disease") out of a previously searched defined group ("biological condition"), as set forth in the application, for example, at page 8 of the originally filed specification. Appellants further note that, even prior to the amendment of November 16, 2007, claim 20 included the step of "defining disease characteristics," including medical tests, and risk characteristics. Likewise, dependent claim 23 recited specific "disease characteristics."

In conclusion, appellants request that the Board direct the entry of the amendment filed on November 16, 2007, and allowance of claims 20-26 and 28. These claims represent a small subset of the currently pending claims. They have been amended on several occasions to comply with numerous Office Actions that represent the views of two different Examiners. Extensive work and thought have gone into being completely responsive to these Examiners, and appellants would like the patent application to be allowed. If allowance is not possible at this stage, appellants ask for the Board's guidance on how to make the claims compliant with any remaining grounds for rejection, so that a patent may be granted that protects appellants' ongoing commercial efforts at a U.S.-based company, and substantial personal and financial investment.

Commissioner is hereby authorized to charge the required Appeal fee of $500, to Deposit Account No. 04-0258. If additional fees are believed necessary, the

Commissioner is further authorized to charge any deficiency or credit any overpayment to Deposit Account No. 04-0258.

Respectfully submitted,
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VIII. APPENDIX OF CLAIMS INVOLVED IN THE APPEAL

1. A computer implemented method for the identification of a drug target associated with a selected biological condition, comprising:

using a computer to analyze stored data related to medical histories of a population;

using a computer to analyze stored data related to medical test results for the population; and

based on computer analysis of the data related to the medical histories and the data related to the medical test results, classifying the population into at least two phenotypic sub populations defined as

at risk and affected (*ARA*), whose members have ever been affected by the selected biological condition, and

at risk and unaffected (*ARU*), whose members ought to be affected by the selected biological condition at the present time based on a risk analysis, but are unaffected by the selected biological condition at the present time;

performing a computer analysis of genetic data from the ARA sub population and the ARU sub population to identify genetic variations therebetween;

displaying the data for a user; and

using data related to the identified genetic variations between the ARA sub population and the ARU sub population to identify the drug target associated with the selected biological condition.

2. The method of claim 1, further comprising generating statistical data related to the medical histories and the medical test results wherein classifying the population comprises analyzing the statistical data.

3. The method of claim 1 wherein analyzing medical histories comprises assigning numerical scores to selected conditions associated with the selected biological condition.

4. The method of claim 1 wherein analyzing medical test results comprises assigning numerical scores to selected medical tests associated with the selected biological condition.

5. The method of claim 1 wherein analyzing medical histories and medical test results comprises assigning numerical scores to selected conditions associated with the selected biological condition and analyzing medical test results comprises assigning numerical scores to selected medical tests associated with the selected biological condition.

6. The method of claim 5 wherein classifying the population comprises evaluating the numerical scores for the medical histories and the medical test results.

7. The method of claim 6 wherein classifying the population comprises combining the numerical scores for the medical histories and the medical test results and classifying the population based on the combined numerical scores.

8. The method of claim 5, further comprising generating statistical data related to the numerical scores for the medical histories and the medical test results wherein classifying the population comprises analyzing the statistical data.

9. The method of claim 8 wherein the statistical data comprises generating a frequency distribution plot related to the numerical scores for the medical histories and the medical test results.

10. The method of claim 1, further comprising comparing the medical histories and the medical test results of the sub population classified as *ARU* with the medical histories and the medical test results of the sub population classified as *ARA*.

11-13 (Cancelled)

14. The method of claim 1, further comprising selecting the portion of the sub population classified as *ARA* and using the selected portion as a control group.

15. The method of claim 1 wherein classifying the population further comprises classifying the population into the ARA sub population, the *ARU* sub population or a phenotypic sub population defined as unknown risk and unaffected (*URU*) by the selected biological condition.

16. The method of claim 15, further comprising comparing the medical histories and the medical test results of the sub population classified as *ARU* with the medical histories and the medical test results of the sub population classified as *URU*.

17. The method of claim 15 wherein the medical test results comprises genetic test results, the method further comprising comparing the genetic test results of

the sub population classified as *ARU* with the genetic test results of the sub population classified as *URU*.

18. The method of claim 17, further comprising determining genetic differences between genetic test results of the sub population classified as *ARU* with the genetic test results of the sub population classified as *URU*.

19. The method of claim 18, further comprising identifying drug targets based on the genetic differences between genetic test results of the sub population classified as *ARU* with the genetic test results of the sub population classified as *URU*.

20. A computer implemented method of data analysis to identify a target for use in treating a selected biological condition, comprising:

defining disease characteristics of the selected biological condition, including medical tests associated with the selected biological condition;

performing a computer analysis of medical test results based on medical tests performed on biological samples from a plurality of subjects with respect to the defined characteristics of the selected biological condition;

based on the analysis, determining an affected status of each of the plurality of subjects;

defining risk characteristics of the selected biological condition;

based on the risk characteristics, determining a risk status of each of the plurality of subjects;

based on the affected status and the risk status, classifying each of the plurality of subjects into a predetermined category for the selected biological condition selected from a group comprising at risk, affected (ARA), whose members have ever been affected by the selected biological condition, and at risk, unaffected (ARU), whose members remain unaffected by the selected biological condition and whose unaffected status is inconsistent with the risk status;

performing genetic tests on the plurality of subjects;

analyzing the genetic test results of the group of subjects classified as ARU with the genetic test results of the group of subjects classified as ARA to determine genetic differences between genetic test results of the group of subjects classified as ARU with the genetic test results of the group of subjects classified as ARA; and

identifying one or more targets for use in treating the selected biological condition.

21. The method of claim 20 wherein the defined disease characteristics of the selected biological condition have associated numerical scores and determining the affected status of each of the plurality of subjects comprises determining numerical scores based on the analysis of the medical test results.

22. The method of claim 20 wherein the defined risk characteristics of the selected biological condition have associated numerical scores and determining the risk status of each of the plurality of subjects comprises determining numerical scores.

23. The method of claim 20 wherein the defined disease characteristics of the selected biological condition have associated numerical scores and the defined risk characteristics of the selected biological condition have associated numerical scores, the classification of each of the plurality of subjects into a predetermined category being based on the numerical scores for affected status and risk status.

24. The method of claim 23 wherein the numerical scores for affected status and risk status are combined to form a combined numerical score, the classification of each of the plurality of subjects into a predetermined category being based on the combined numerical scores for affected status and risk status.

25. The method of claim 20 wherein the medical tests associated with the selected biological condition have varying degrees of relevance in defining the disease characteristics, the method further comprising assigning relevance weighting factors to the medical tests based on the degree of relevance, the affected status being based on the weighted medical tests.

26. The method of claim 20, further comprising generating statistical data related to the affected status and risk status wherein classifying each of the plurality of subjects into a predetermined category comprises analyzing the statistical data.

27. (Cancelled)

28. The method of claim 20 wherein risk status is determined at least in part from medical histories of the plurality of subjects, the method further comprising comparing the medical histories and the medical test results of the group of subjects

classified as *ARU* with the medical histories and the medical test results of the group of subjects classified as *ARA*.

29-30. (Cancelled)

31. The method of claim 20 wherein identifying one or more targets comprises identifying a drug target based on the genetic differences between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *ARA*.

32. The method of claim 20 wherein identifying one or more targets comprises identifying a diagnostic assay based on the genetic differences between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *ARA*.

33. The method of claim 20 wherein identifying one or more targets comprises identifying a vaccine based on the genetic differences between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *ARA*.

34. The method of claim 20 wherein the plurality of subjects are classified into a category selected from a group comprising at risk, affected (*ARA*), unknown risk, unaffected (*URU*), and at risk unaffected (*ARU*).

35. The method of claim 34 wherein risk status is determined at least in part from medical histories of the plurality of subjects, the method further comprising comparing the medical histories and the medical test results of the group of subjects classified as *ARU* with the medical histories and the medical test results of the group of subjects classified as *URU*.

36. The method of claim 34 wherein the medical test results comprises genetic test results, the method further comprising comparing the genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *URU*.

37. The method of claim 36, further comprising determining genetic differences between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *URU*.

38. The method of claim 37, further comprising identifying a drug target based on the genetic differences between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *URU*.

39. The method of claim 38, further comprising identifying a diagnostic assay based on the genetic differences between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *URU*.

40. The method of claim 38, further comprising identifying a vaccine based on the genetic differences between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *URU*.

41. A system for data analysis to identify a target for treating a selected biological condition, comprising:

a affected status data structure containing numerical data defining disease characteristics of the selected biological condition, including medical tests associated with the selected biological condition;

a disease risk data structure containing numerical data defining disease risk characteristics of the selected biological condition; and

a processor to:

accept medical test results from a plurality of subjects and assign affected status numeric scores to the medical test results based on the numerical data defining disease characteristics of the selected biological condition;

store the affected status numeric scores for each of the subjects in the affected status data structure;

accept medical history data from a plurality of subjects and assign current disease risk numeric scores to the medical history data based on the numerical data defining disease risk characteristics of the selected biological condition;

store the disease risk numeric scores for each of the subjects in the disease risk data structure;

determine an affected status and risk status for each of the subjects based on the respective affected status numeric scores and the current disease risk numeric scores:

based on the affected status and the risk status, classify each of the plurality of subjects into a predetermined category selected from a group of categories comprising at risk, affected (ARA) and at risk unaffected (ARU);

analyze genetic test result data to determine genetic differences between the subjects in the ARA category and subjects in the ARU category; and

identify a target for treating the selected biological condition.

42. The system of claim 41 wherein the processor combines the numerical scores for affected status and risk status to form a combined numerical score, the processor further classifying of each of the plurality of subjects into a predetermined category being based on the combined numerical scores for affected status and risk status.

43. The system of claim 41 wherein the medical tests associated with the selected biological condition have varying degrees of relevance in defining the disease characteristics, the processor further assigning relevance weighting factors to the medical tests based on the degree of relevance, the processor determining the affected status based on the weighted medical tests.

44. The system of claim 41 wherein the processor further generates statistical data related to the affected status and risk status, the processor further classifying of each of the plurality of subjects into a predetermined category being based on the combined numerical scores for affected status and risk status based on analysis of the statistical data.

45. (Cancelled)

46. The system of claim 41 wherein the processor further classifies each of the plurality of subjects into a predetermined category selected from a group of categories comprising at risk, affected (*ARA*), unknown risk, unaffected (*URU*), and at risk unaffected (*ARU*).

47. The method of claim 1 wherein identifying a target comprises identifying a drug target based on the genetic variations between genetic test results of the group of

subjects classified as *ARU* with the genetic test results of the group of subjects classified as *ARA*.

48. The method of claim 1 wherein identifying a target comprises identifying a diagnostic assay based on the genetic variations between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *ARA*.

49. The method of claim 1 wherein identifying a target comprises identifying a vaccine based on the genetic variations between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *ARA*.

50. The method of claim 1 wherein identifying a target comprises identifying a candidate drug based on the genetic variations between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *ARA*.

51. The method of claim 20 wherein identifying a target comprises identifying a candidate drug based on the genetic variations between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *ARA*.

52. The system of claim 41 wherein the processor is configured to identify a drug target based on the genetic variations between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *ARA*.

53. The system of claim 41 wherein the processor is configured to identify a candidate drug based on the genetic variations between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *ARA*.

54. The system of claim 41 wherein the processor is configured to identify a diagnostic assay based on the genetic variations between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *ARA*.

55. The system of claim 41 wherein the processor is configured to identify a vaccine based on the genetic variations between genetic test results of the group of subjects classified as *ARU* with the genetic test results of the group of subjects classified as *ARA*.

56. A computer implemented method for the classification of a population for evaluation of a selected biological condition, comprising:

defining risk characteristics associated with the selected biological condition;

storing data associated with the defined risk characteristics;

defining affected status indicators for the selected biological condition;

storing data associated with the defined affected status indicators;

using the stored data to classify a study population based on the defined risk characteristics and the defined affected status indicators to thereby classify individual ones of the subjects in the study population as at risk and affected (ARA) by the selected biological condition, the ARA individuals having a risk status indicating the expectation that the individuals are at significant risk for having the selected biological condition at the present time, and an affected status indicating that the ARA individuals are presently affected by the selected biological condition, and to classify individual ones of the subjects in the study population as at risk and unaffected (ARU) by the selected biological condition, the ARU individuals having a risk status indicating the expectation that the individuals are at significant risk for having the selected biological condition at the present time, and an unaffected status indicating that the ARU individuals are presently not affected by the selected biological condition.

57. A computer implemented method for the classification of a population for evaluation of a selected biological condition, comprising:

selecting a study population to be classified into subpopulations selected from a group of subpopulations comprising:

at risk and affected (*ARA*), whose members have a risk status indicating the expectation that the members are at significant risk for having the selected biological condition at the present time, and an affected status indicating that the members of the ARA subpopulation are presently affected by the selected biological condition;

at risk and unaffected (ARU) by the selected biological condition, whose members have a risk status indicating the expectation that the members are at significant risk for having the selected biological condition at the present time, and an affected status indicating that the ARU individuals are presently not affected by the selected biological condition, and

unknown risk and unaffected (URU) by the selected biological condition, whose members have an indeterminate risk status for having the selected biological condition at the present time, and an affected status indicating that the URU individuals are presently not affected by the selected biological condition;

the size of the study population being selected so that the number of potential ARU members provides 95% confidence to detect alleles represented at at least 1% frequency in the ARU sub population; and

based on computer analysis of the data related to the medical histories and the data related to the medical test results, classifying the study population into the ARA, ARU or URU sub populations to permit evaluation of the selected biological condition by analyzing at least two of the subpopulations.

58. The method of claim 57, further comprising:

performing a computer analysis of genetic data from the ARA sub population and the ARU sub population to identify genetic variations therebetween; and

using data related to the identified genetic variations between the ARA sub population and the ARU sub population to identify a drug target associated with the selected biological condition.

59. A method for the classification of a population for evaluation of a selected biological condition, comprising:

defining risk characteristics associated with the selected biological condition;

defining affected status indicators for the selected biological condition;

classifying a study population based on the defined risk characteristics and the defined affected status indicators to thereby classify individual ones of the subjects in the study population as at risk and affected (ARA) by the selected biological condition, the ARA individuals having a risk status indicating the expectation that the individuals are at significant risk for having the selected biological condition at the present time, and

an affected status indicating that the ARA individuals are presently affected by the selected biological condition, and to classify individual ones of the subjects in the study population as at risk and unaffected (ARU) by the selected biological condition, the ARU individuals having a risk status indicating the expectation that the individuals are at significant risk for having the selected biological condition at the present time, and an affected status indicating that the ARU individuals are presently not affected by the selected biological condition, the size of the study population being selected so that the number of potential ARU members provides 95% confidence to detect alleles represented at at least 1% frequency in the ARU sub population.

60. A computer implemented method for the classification of a population for evaluation of a selected biological condition, comprising:

defining risk characteristics associated with the selected biological condition;

storing data associated with the defined risk characteristics;

defining affected status indicators for the selected biological condition;

storing data associated with the defined affected status indicators;

using the stored data to classify a study population based on the defined risk characteristics and the defined affected status indicators to thereby classify individual ones of the subjects in the study population as at risk and affected (ARA) by the selected biological condition, the ARA individuals having a risk status indicating that the individuals are expected to be affected by the selected biological condition at the present time, and an affected status indicating that the ARA individuals are presently affected by the selected biological condition, and to classify individual ones of the subjects in the study population as at risk and unaffected (ARU) by the selected biological condition, the ARU individuals having a risk status indicating that the individuals are expected to be affected by the selected biological condition at the present time, and an affected status indicating that the ARU individuals are presently not affected by the selected biological condition.

61. A computer implemented method for the identification of a population phenotypically unaffected by a selected biological condition, comprising:

defining risk characteristics associated with the selected biological condition;

storing data associated with the defined risk characteristics;

defining affected status indicators for the selected biological condition;

storing data associated with the defined affected status indicators;

using the stored data to identify individuals as phenotypically affected by the selected biological condition and to identify individuals as phenotypically unaffected by the selected biological condition despite a risk status consistent with risk status associated with individuals identified as phenotypically affected by the selected biological condition.

IX. EVIDENCE APPENDIX

Pursuant to 37 C.F.R. § 41.37(c)(1)(ix) the following evidence under 37 C.F.R. § 1.130. 1.131 or 1.132 is relied upon in this Appeal Brief.

1. Affidavit of Dr. Shawn Iadonato filed December 18, 2006. This Affidavit under 37 C.F.R. § 1.132 was made of record and considered by the Examiner. See Office Action dated May 16, 2007, page 22, lines 16-20.

2. Second Affidavit of Dr. Shawn Iadonato filed February 22, 2007. This Affidavit under 37 C.F.R. § 1.132 was made of record and considered by the Examiner. See Office Action dated May 16, 2007, page 2, lines 16-20.

3. Affidavit of Dr. Cammie Lesser dated December 15, 2006. This Affidavit under 37 C.F.R. § 1.132 was made of record and considered by the Examiner. See Office Action dated May 16, 2007, page 19, lines 20-21.

4. Affidavit of Dr. Richard Myers dated December 16, 2006 This Affidavit under 37 C.F.R. § 1.132 was made of record and considered by the Examiner. See Office Action dated May 16, 2007, page 15, lines 13-14.

5. Press release dated December 26, 2007 entitled, "Cubist Pharmaceuticals Acquires Illumigen Biosciences; Expects to File IND for Lead HCV Compound IB657 in 2008." This document is not of record because the event did not take place until after appellants filed the most recent response in the prosecution history, on November 16, 2007.

EXPRESS MAIL NO. EV737280603US

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Charles L. Magness and Shawn P. Iadonato
Application No.	:	09/707,576
Filed	:	November 6, 2000
For	:	SYSTEM AND METHOD FOR SELECTIVELY CLASSIFYING A POPULATION

Examiner	:	Anna Skibinsky
Art Unit	:	1631
Docket No.	:	55382-3
Date	:	February 24, 2006

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Affidavit of Shawn Iadonato, Ph.D. under 37 C.F.R. § 1.132

I, Shawn Iadonato, Ph.D. being duly sworn, say:

1. I am an internationally recognized scientist and at the time of filing the above-referenced patent application I was employed as Vice-President and Chief Scientific Officer, at Illumigen Biosciences, Inc., Seattle, WA. I received a Bachelors Degree in Biology from the University of Pennsylvania in Philadelphia and a Ph.D. degree from in Genetics from the University of Washington.

2. I am an author or co-author of numerous peer-reviewed research articles and have been invited to give numerous presentations on my research at national and international meetings. Prior to joining Illumigen, I managed sequence data collection

for the University of Washington Genome Center. My curriculum vitae is attached as Exhibit 1.

3. In my capacity as Founder, Vice-President, and Chief Scientific Officer, I manage the scientific and drug development programs of Illumigen. I have more than eight years experience developing and managing large-scale genetics and genomics projects, most notably involving my work on the Human Genome Project.

4. On information and belief, claims of the present application have been rejected under 35 U.S.C. § 112, first paragraph. According to the Office Action dated September 29, 2005, claims 1-10, 14-26, 28, 31-44 and 46-55 fail to comply with the enablement requirement because allegedly there is "undue experimentation required to go from the classification results achieved by implementing the invention to drug target identification without some prior knowledge of a relationship between a potential target and a biological condition as claimed." The experiments and results described in paragraphs 5-12 below support the enablement of the claimed invention by showing clearly that undue experimentation was not required to identify a drug target using the methods of the invention.

5. Illumigen's first drug is an anti-viral therapy for hepatitis C, and the drug is undergoing important pre-clinical studies; Phase I trials are scheduled for 2007. The drug was developed by following the methods as explicitly described in the present patent application.

6. In Step 1, recruiting of patients was performed from among populations at high risk for hepatitis C infection, specifically intravenous drug users and hemophiliacs. Over 3,500 subjects were screened, and a group of serially exposed and seronegative subjects was identified. These subjects correspond exactly to the ARU "at risk, unaffected" population of the claims and the specification.

7. In Step 2, we sequenced a fraction of the genome of case (ARU) and control (ARA and URU) subjects. These control subjects correspond exactly to the at

risk and affected (exposed to hepatitis C and currently infected with the virus) and unknown risk and unaffected (no exposure data and not currently infected with the virus) populations of the application and claims. Using the computer-based methods exactly as disclosed in the application, genetic association analysis was performed, and a mutation associated with the "at risk and unaffected" ARU group was identified. This mutation affects a protein which corresponds to the "target" of the claims and the specification. Thus, the target was identified solely by the computer-based analysis.

8. The mutation affects a gene involved in the interferon pathway; the gene encodes a protein known as OAS1. Using the information that mutated forms of OAS1 were expressed in the ARU group but not the ARA group, we developed an optimized form of the protein expressed by the mutated gene and tested it in an *in vitro* model of HCV infection; this protein corresponds to the therapeutic of the specification and the claims. As shown in Exhibit 2, the therapeutic protein, referred to as IB657, inhibits EMCV infection of hepatoma (Huh7) cells.

9. On information and belief, the Office Action at page 11, lines 6-8, alleges that "the method of identifying a drug target based on genetic differences between two groups is not trivial and requires years to complete..." Although I agree that identifying a drug target is not "trivial," as it in fact is a major breakthrough, I strongly disagree that it takes years to complete. By following the methods described in this application, we identified a drug target (the mutated gene OAS1) and a drug in three years from start to preclinical drug candidate. A single cycle of data input, review and analysis according to the invention led directly to this drug discovery.

10. On information and belief, the Office Action at page 7, lines 6-10, alleges that "the identification of a drug target requires knowledge of the cause of disease and the biological systems associated with it. Drug target identification currently requires several months to years of research and costs millions of dollars per drug." The operative word here is currently. What applicants have disclosed and claimed is not the current method of target and drug discovery, but new methods. The drug currently

undergoing preclinical testing, as described in paragraph 9 above, was developed at a cost of, at most, 10% of the conventional approach. Furthermore, in addition to the cost benefit, the drug has entirely different toxicity parameters. The drug is based on studying ARU populations who already express a version of the drug and enjoy the beneficial effects of having it in their system. Therefore, the drug we developed is expected to have negligible toxicity compared to traditional drugs based on synthetic chemistry approaches.

11. The drug that is the subject of paragraphs 9 and 10 above is one of many polypeptides disclosed and claimed in our subsequent co-pending patent application, Serial No. 10/972,135. That application was granted Special Status in a Decision on Petition granted on December 7, 2005. The ground for the Petition was that applicant Illumigen is a Small Entity and the subject matter of the application is a major asset of the company.

12. The Small Entity status of the company and the granting of the Petition to Make Special in the co-pending application are further evidence that the present patent application is fully enabling, because the target and the drug were discovered in less than three years through the work of far fewer employees, and using far fewer resources and expenses, as compared to drug discovery at a traditional pharmaceutical company.

I further declare that all statements made herein of my own knowledge are true and that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code.

Shawn Iadonato, Ph.D.

State of Washington)
) ss.
County of *King*)

On this 22nd day of February, 2006, before me, a Notary Public in and for the State and County aforesaid, personally appeared Shawn Iadonato, Ph.D. to me known and known to me to be the person of that name, who signed and sealed the foregoing instrument, and he acknowledged the same to be his free act and deed.

Notary Public SHANNON ELISE LEIGHTON
MY APPOINTMENT EXPIRES: 5-25-08

Commission expires_____

EXPRESS MAIL NO.
EB 069600865 US

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Charles L. Magness and Shawn P. Iadonato
Application No.	:	09/707,576
Filed	:	November 6, 2000
For	:	SYSTEM AND METHOD FOR SELECTIVELY CLASSIFYING A POPULATION

Examiner	:	Anna Skibinsky
Art Unit	:	1631
Docket No.	:	55382-3
Date	:	February 9, 2007

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Affidavit of Shawn Iadonato, Ph.D. under 37 C.F.R. § 1.132

I, Shawn Iadonato, Ph.D. being duly sworn, say:

1. I am an internationally recognized scientist and at the time of filing the above-referenced patent application I was employed as Vice-President and Chief Scientific Officer, at Illumigen Biosciences, Inc., Seattle, WA. I received a Bachelors Degree in Biology from the University of Pennsylvania in Philadelphia and a Ph.D. degree in Genetics from the University of Washington.

2. I am an author or co-author of numerous peer-reviewed research articles and have been invited to give numerous presentations on my research at national and international meetings. Prior to joining Illumigen, I managed sequence data collection

for the University of Washington Genome Center. My curriculum vitae is attached as Exhibit 1.

3. In my capacity as Founder, Vice-President, and Chief Scientific Officer, I manage the scientific and drug development programs of Illumigen. I have more than eight years experience developing and managing large-scale genetics and genomics projects, most notably involving my work on the Human Genome Project.

4. On information and belief, claims of the present application have been rejected under 35 U.S.C. § 112, first paragraph. According to the Office Action dated June 16, 2006, claims 1-10, 14-26, 28, 31-44 and 46-55 fail to comply with the enablement requirement because allegedly there is "undue experimentation required to go from the classification results achieved by implementing the invention to drug target identification without some prior knowledge of a relationship between a potential target and a biological condition as claimed." The experiments and results described in paragraphs 5-12 below support the enablement of the claimed invention by showing clearly that undue experimentation was not required to identify a drug target using the methods of the invention. In fact, following the methods of the present invention in a hepatitis C study, we found more than one drug target. The first of these was identified in an extremely short period of laboratory work (see 8. below) thus supporting the claim that the invention was sufficiently enabled.

5. Illumigen's first drug is an anti-viral therapy for hepatitis C, and the drug is undergoing important pre-clinical studies; Phase I trials are scheduled for 2007. The drug was developed by following the methods as explicitly described in the present patent application.

6. In Step 1, recruiting of patients was performed from among populations at high risk for hepatitis C infection, specifically intravenous drug users and hemophiliacs. Over 3,500 subjects were screened, and a group of serially exposed and seronegative subjects was identified. These subjects correspond exactly to the ARU "at risk, unaffected" population of the claims and the specification.

7. In Step 2, we sequenced a fraction of the genome of case (ARU) and control (ARA) subjects. These case and control subjects correspond exactly to the at risk and unaffected (exposed to hepatitis C and not currently infected with the virus) and at risk and affected (exposed to hepatitis C and currently infected with the virus) populations of the application and claims. Using the computer-based, genetic association methods like those disclosed in the application, genetic mutations associated with the "at risk and unaffected" ARU group were identified. These mutations affect a protein which corresponds to the "target" of the claims and the specification.

8. The mutations identified in step 2 of paragraph 7 above was discovered in a very short period of time with minimal resources, supporting the enablement of the methods of the invention. Illumigen's laboratory only began operation in January, 2003 and initiated DNA sequence analysis of the ARU and ARA groups in March, 2003. On October 23, 2003, a provisional application was submitted to the USPTO concerning our first drug target and detailing the primary functional mutation. The laboratory work supporting the computational genetic analysis was conducted using a single sequencing instrument and approximately one full-time-equivalent laboratory technician. Thus, while additional validating analyses were conducted after this date and drug optimization and testing has occurred over the succeeding three years, the limited amount of laboratory work that was conducted for primary identification of a drug target is highly supportive of enablement.

9. The mutation affects a gene involved in the interferon pathway; the gene encodes a protein known as OAS1. Using the information that mutated forms of OAS1 were homozygously expressed significantly more frequently in the ARU group as compared with the ARA group, we developed an optimized form of the protein derived from the mutated gene and tested it in an *in vitro* model of HCV infection; this protein corresponds to the therapeutic of the specification and the claims. As shown in Exhibit 2, the therapeutic protein, referred to as IB657, inhibits EMCV infection of hepatoma

(Huh7) cells.

10. On information and belief, the Office Action at page 10, lines 16-17, alleges that "the method of identifying a drug target based on genetic differences between two groups is not trivial and requires years to complete..." Although I agree that identifying a drug target is not "trivial," as it is in fact a major breakthrough, I strongly disagree that it takes years to complete. By following the methods described in this application, we identified a drug target (the mutated gene OAS1) initially in about six months and a drug in three years from start to preclinical drug candidate. A single cycle of data input, review and analysis according to the invention led directly to this drug discovery.

11. On information and belief, the Office Action at page 10, lines 14-15, alleges that "the identification of a drug target requires the sorting out of 1000's of targets present in most organisms." What applicants have disclosed and claimed is not the current method of target and drug discovery, but new methods. The drug currently undergoing preclinical testing, as described in paragraph 9 above, was developed at a fractional cost of the conventional approach. Furthermore, in addition to the cost benefit, the drug has entirely different toxicity parameters. The drug is based on studying ARU populations who already express a version of the drug and enjoy the beneficial effects of having it in their system. Therefore, the drug we developed is expected to have negligible toxicity compared to traditional drugs based on synthetic chemistry approaches. Thousands of targets were not "sorted out." The ARA and ARU comparison of the invention obviates that kind of historically laborious effort.

12. The drug that is the subject of paragraphs 9 and 10 above is one of many polypeptides disclosed and claimed in our subsequent co-pending patent application, Serial No. 10/972,135. The polypeptide of SEQ ID NO:48 has been found to be free of the art.

13. The 10/972,135 application was granted Special Status in a Decision on

Petition granted on December 7, 2005. The ground for the Petition was that applicant Illumigen is a Small Entity and the subject matter of the application is a major asset of the company. The Small Entity status of the company and the granting of the Petition to Make Special in the co-pending application are further evidence that the present patent application is fully enabling, because the target and the drug were discovered in less than three years through the work of far fewer employees, and using far fewer resources and expenses, as compared to drug discovery at a traditional pharmaceutical company.

I further declare that all statements made herein of my own knowledge are true and that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code.

Shawn Iadonato, Ph.D.

State of Washington)
) ss.
County of *King*)

On this 9th day of February, 2006, before me, a Notary Public in and for the State and County aforesaid, personally appeared Shawn Iadonato, Ph.D. to me known and known to me to be the person of that name, who signed and sealed the foregoing instrument, and he acknowledged the same to be his free act and deed.

TERRI RAY NOTARY PUBLIC COMMISSION EXPIRES 10-29-08 STATE OF WASHINGTON

Notary Public Terri Ray

Commission expires 10/29/08

EXPRESS MAIL NO.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Charles L. Magness and Shawn P. Iadonato
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Examiner	:	Anna Skibinsky
Art Unit	:	1631
Docket No.	:	55382-3
Date	:	December 16, 2006

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Affidavit of Richard M. Myers, Ph.D. under 37 C.F.R. § 1.132

I, Richard M. Myers, Ph.D. being duly sworn, say:

1. I am an internationally recognized scientist and I am employed as Chairman of the Department of Genetics, Stanford University School of Medicine. I also hold positions as Stanford W. Ascherman Professor of Genetics, and Director, Stanford Human Genome Center, both in the Department of Genetics at Stanford University School of Medicine. I received a Bachelors Degree in Biochemistry in 1977 from the University of Alabama, and a Ph.D. degree in Biochemistry in 1982 from the University of California at Berkeley. I currently serve on the Scientific Advisory Board of Illumigen Biosciences, Inc.

2. I am an author or co-author of over 130 peer-reviewed research articles and I have been invited to give presentations on my research at national and international meetings. I was a founding scientist of Mercator Genetics, Inc., and an original member of the scientific advisory board of Genaissance Pharmaceuticals. I am the recipient of several awards related to my work in genetics and the human genome, including the Wills Foundation Award, 1986-2005; the Pritzker Foundation Award, in 2002; and the Searle Scholar Program, from 1987-1990. These and other awards, as well as the details of my publications, are listed in my curriculum vitae, which is attached as Exhibit 1.

3. On information and belief, claims of the present application have been rejected under 35 U.S.C. § 112, first paragraph. According to the Office Action dated June 16, 2006, claims 1-10, 14-26, 28, 31-44 and 46-55 fail to comply with the enablement requirement because allegedly there is "undue experimentation required to go from the classification results achieved by implementing the invention to drug target identification without some prior knowledge of a relationship between a potential target and a biological condition as claimed." It is my opinion that the methods described in the application taken together with the state of the art at the time of the application support the enablement of the claimed invention. As discussed below, I conclude that undue experimentation would not be required to identify a drug target using the methods of the invention.

4. On information and belief, the Office Action at page 6, lines 3-4, alleges that "there would be an unpredictable amount of experimentation required to practice the claimed invention." Inasmuch as the methods of the present invention relate to epidemiological, statistical, and genetics analyses, I disagree that the amount of "experimentation" is unpredictable. In fact, I disagree with use of the term experimentation as the much of the genetics work (that the examiner appears to believe not enabled in the application) is routine. In my work as a federally funded scientist, like others in my field, I am routinely required to predict the amount of effort required in my proposals to funding agencies. Additionally, over a nine year period, I was a standing

member of two National Institutes of Health sStudy Sections (and Chair of one of them) that review proposals from scientists representing a broad cross-section of skill in these arts. Following that, I was a member for four years of the Advisory Council—the group of experts that give the final sign-off for funding decisions to the Director—of the National Human Genome Research Institute (one of the NIH institutes). In my experience, it is routine for such proposals to make predictions with reasonable accuracy about the amount of effort required for studies similar to those required by the claimed invention.

5. On information and belief, the Office Action at page 10, lines 15-17, alleges that "the method of identifying a drug target based on genetic differences between two groups is not trivial and requires years to complete...." Although I agree that identifying a drug target is not "trivial," I disagree that it would require years to complete if the claimed methods are followed. Based on my scientific knowledge of molecular genetics and infectious disease, I am familiar with the methods routinely used to identify mutations in genes and to correlate these mutations with protein expression. My own research involves the study of the structure, function and evolution of the human genome, and I design and perform experiments to understand the role of genes in human diseases. In the course of my career spanning over two decades, I have worked closely with numerous scientists of varying levels of training and expertise, and I have collaborated with laboratories of several foreign countries. I also serve as Editor of the publication *Genome Research*, so I am familiar with the skill level of scientists in my areas of expertise. It is my opinion that anyone of ordinary skill in the field of molecular genetics would have a comparable level of familiarity and expertise.

6. I am aware that it is possible and routine to identify a mutation without knowledge of the underlying disease mechanism, and to determine whether that mutation corresponds to phenotypic characteristics of a subpopulation, such as the "at risk unaffected". For example, I work in the areas of brain and cardiovascular phenotypes as well as infectious diseases, and I study the role of genes in these and other diseases. In these areas and more, it is routine to identify genetic mutations

associated with phenotypic characteristics (e.g. inherited diseases) without previous knowledge of a relationship to the biological condition. In the context of the claim language and the patent specification, I understand that a population "at risk" could be a population exposed to an infectious agent, a subpopulation "at risk and affected" would be a population exhibiting a phenotypic trait, such as evidence of infection, and that a subpopulation "at risk and unaffected" would be a population expected to have the disease on the basis of history of exposure, yet not exhibiting phenotypic evidence of the infection (*i.e.* symptomatic, serum antibodies, *etc.*).

7. As a scientist working closely with physicians and epidemiologists to study the genetic basis of human disease, I am aware of the procedures and requirements for identifying matched individuals for conducting risk analysis of infections and other diseases. In my opinion, identifying "at risk unaffected" and "at risk affected" populations, and obtaining biological samples, such as blood samples, is routine and need not be time-consuming. Such samples are routinely obtained in the course of medical examination and diagnosis. Using well-known methods of sequence analysis and mutation identification, it is entirely feasible and within ordinary skill in this art to identify a genetic difference that correlates with the affected versus unaffected phenotype. Then, using the vast resources available in the gene databases, including sequences obtained as a result of the Human Genome Project, it would not require undue experimentation to identify a protein or regulatory region that correlates with the observed genetic difference. Indeed, I have either led or been actively involved in several studies that identified DNA sequence variants that are associated with human diseases, including an inherited form of childhood epilepsy, hemochromatosis, basal cell nevus syndrome (of which skin cancer is a symptom), and several others. I participated in the Human Genome Project from its inception, and my laboratory was funded to collaborate on the sequencing of human chromosomes 5, 16 and 19. As a result of this work, I am familiar with the use of the human genome sequences and their availability and utility to anyone of ordinary skill in this art.

8. On information and belief, the Office Action at page 7, lines 2-3, alleges that "the claims are broad in that they are drawn to identification of a drug target for any given biological condition." Based upon my experience and the prior art, it is my belief that the methods of the claimed invention are broadly applicable; certainly applicable beyond simply infectious disease.

9. On information and belief, the Office Action at page 8, line 18, alleges "a polypeptide is not a drug target" as a rationale for not accepting applicant's prior supportive arguments. I strongly disagree with this position and submit that entire classes of important drugs (e.g. monoamine oxidase inhibitors and angiotensin converting enzyme (ACE) inhibitors) act on polypeptide drug targets. In fact, most small molecule drugs are inhibitors of proteins, thus making the proteins themselves the drug targets. Furthermore, there are well-known polypeptide therapies (e.g. insulin and growth hormone) where a polypeptide is the drug itself.

10. On information and belief, the Office Action at page 10, lines 4-5, alleges that "the details for identifying a drug target based on the classification are not described. Thus, there is not sufficient support to enable one skilled in the art of make or use the invention." I strongly disagree with this statement for the following reasons. First, applicants do describe general methods to identify functional mutations differentially associated with the ARU and ARA groups. Second, association methods for identifying genetic mutations, such as those described by example in the application, have been well known in the art since the 1990s. Third, identification of such mutations by comparison with the "at risk unaffected" group that de facto identifies a target. This latter point is in contrast to the traditional analysis using only "at risk affected" groups for disease gene identification which does not generally identify a target.

11. It is an advantage of the present methods that no traditional biochemical screening is required. I am well-qualified to provide an opinion on the differences between traditional biochemistry-based screening, and the new methods disclosed and claimed in this patent application. Instead, screening is performed by computer by

comparing the polynucleotides from the "at risk affected" and "at risk unaffected" groups. One of ordinary skill will be familiar with the input of data from human samples and the methods and search parameters for identifying genetic differences between two samples. This genetic, information-based analysis is a far more efficient, fast, and cost-effective method of identifying the relevant biochemical difference or differences between at-risk populations with and without the disease. It is the comparison of the observed genetic difference (*e.g.* point mutation, deletion, insertion) with the database to pinpoint the modified region and identify the function that leads directly to identification of a target.

12. On information and belief, the Office Action at page 10, lines 14-15, alleges that "identification of a drug target requires the sorting out of 1000's of targets present in most organisms." Based upon my knowledge of genetics and my direct experience in the field over the course of the past two decades, this statement is incongruous with the history of biomedical research.

13. In conclusion, I am a person with knowledge of the ordinary skill in this art, and in my professional capacity I will be a consumer of the new methods provided by the patent application. It is within my ability to understand and follow the claimed methods. For any disease in which the phenotype is related to a genetic difference, I would expect the claimed methods to allow me to discover that difference, and to correlate it with a gene product, such as a protein. That gene product in turn will correlate with the phenotypic difference between "at risk unaffected" (ARU) and "at risk affected" (ARA) individuals. This information will allow me to identify a target around which a treatment could be designed to mimic the protective phenotype of the "at risk unaffected" individuals.

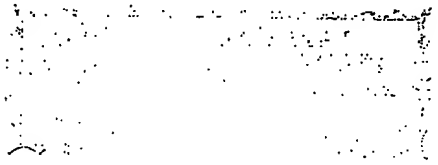
I further declare that all statements made herein of my own knowledge are true and that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code.

Richard M. Myers

Richard M. Myers, Ph.D.

State of California)
San Mateo) ss.
County of ~~Santa Clara~~

On this 16 day of December 2006, before me, a Notary Public in and for the State and County aforesaid, personally appeared Richard M. Myers, ~~Ph.D.~~, to me known and known to me to be the person of that name, who signed and sealed the foregoing instrument, and he acknowledged the same to be his free act and deed.



Notary Public

Commission expires Jan 13th, 2009

EXPRESS MAIL NO.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Charles L. Magness and Shawn P. Iadonato
Application No.	:	09/707,576
Filed	:	November 6, 2000
For	:	SYSTEM AND METHOD FOR SELECTIVELY CLASSIFYING A POPULATION

Examiner	:	Anna Skibinsky
Art Unit	:	1631
Docket No.	:	55382-3
Date	:	December 15, 2006

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Affidavit of Cammie Lesser, M.D., Ph.D. under 37 C.F.R. § 1.132

I, Cammie Lesser, M.D., Ph.D. being duly sworn, say:

1. I am an internationally recognized scientist and I am employed as Assistant Professor at Massachusetts General Hospital/Harvard Medical School in Boston, Massachusetts. I received a Bachelors Degree in Biochemistry from Brown University, a Ph.D. degree in Biochemistry in 1993 from the University of California at San Francisco, and an M.D. degree in 1995 from the University of California at San Francisco.

2. I am an author or co-author of several peer-reviewed research articles and I have been invited to give presentations on my research at national and international

meetings. Prior to joining Massachusetts General Hospital/Harvard Medical School, I was a medical resident at the University of Washington. My curriculum vitae is attached as Exhibit 1.

3. On information and belief, claims of the present application have been rejected under 35 U.S.C. § 112, first paragraph. According to pages 9-10 of the Office Action dated June 16, 2006, claims 1-10, 14-26, 28, 31-44 and 46-55 fail to comply with the enablement requirement because allegedly there is "undue experimentation required to go from the classification results achieved by implementing the invention to drug target identification without some prior knowledge of a relationship between a potential target and a biological condition as claimed." It is my opinion that the methods described in the application support the enablement of the claimed invention. As discussed below, I conclude that undue experimentation would not be required to identify a drug target using the methods of the invention.

4. I am aware that it is possible and routine to identify a mutation without knowledge of the underlying disease mechanism, and to determine whether that mutation corresponds to phenotypic characteristics of a population such as the ARU group. In the context of the claim language and the patent specification, I understand that a population "at risk" could be a population exposed to an infectious agent, a subpopulation "at risk and affected" would be a population exhibiting a phenotypic trait, such as evidence of infection, and that a subpopulation "at risk and unaffected" would be a population expected to have the disease on the basis of history of exposure, yet not exhibiting phenotypic evidence of the infection (*i.e.* symptomatic, serum antibodies, *etc.*). I am also aware that the phenotypic definition of "at risk unaffected" varies from one biological condition to another and this definition allows the breadth of applicability of the present methods to conditions other than infectious disease.

5. As a medical doctor, I am aware of the procedures and requirements for identifying matched individuals for conducting risk analysis of infections and other diseases. In my opinion, identifying "at risk unaffected" and "at risk affected"

populations, and obtaining biological samples, such as blood samples, is routine and need not be time-consuming. Such samples are routinely obtained in the course of medical examination and diagnosis.

6. Based on my scientific knowledge of molecular genetics, I am familiar with the methods routinely used to identify mutations in genes and to correlate these mutations with functional effects, such as modification of protein amino acid sequence. I also appreciate how the identification of such functional genetic variations between ARA and ARU groups directly identifies the gene containing the genetic variations as a drug target. Anyone of ordinary skill in the field of molecular genetics would have a comparable level of familiarity and expertise.

7. On information and belief, the Office Action at page 8, lines 5-7, alleges that "applicants have not described how to identify where the genetic variation associated with the disease exists." The Office Action at page 8, line 21 through page 9, line 2, in a similar argument further alleges "it is not disclosed how the relevant polynucleotide is detected. Additionally, how the functional coding region carrying the genetic difference of interest is located." I disagree with these allegations. Applicants describe in the specification between page 10, line 22 and page 13 line 5, methods for detecting mutations and statistically associating those mutations with the ARA group relative to a control group. Using well-known methods of sequence analysis, mutation identification and statistical genetics, it is entirely feasible and within ordinary skill in this art to identify a genetic difference that correlates with the affected versus unaffected phenotype.

8. On information and belief, the Office Action at page 10, lines 14-15, alleges that "identification of a drug target requires the sorting out of 1000's of targets present in most organisms." I disagree with this statement. It is highly unlikely that few, if any, drug targets have been identified by "sorting out 1000's of targets present in most organisms."

9 On information and belief, what applicants have disclosed and claimed is not the traditional method of target and drug discovery. In fact, an advantage of the present methods is that they are the opposite of traditional methods. The present methods allow identification of a drug target by comparison of the ARA and ARU groups rather than by traditional approaches to drug target discovery. Many of the risk analyses and genetic comparisons outlined by the present methods are also amenable to computer automation. Thus the present methods provide a very effective short-cut to drug target discovery, and allow a researcher to identify relevant differences between the ARA and ARU subjects. The identification of the observed genetic difference (*e.g.* point mutation, deletion, insertion) between the "at risk unaffected" and "at risk affected" groups leads directly to identification of a target. The effect of the observed genetic difference on target function also leads the researcher to the type of required therapeutic intervention (e.g. protein replacement therapy versus antagonistic small molecule).

10. Because the target is identified in humans, the method of the invention provides at least two other differences from and advantages over traditional drug target identification. First, it circumvents much of the laboratory animal experimentation otherwise performed to identify a target. Second, because the at risk unaffected population is healthy, the method teaches development of a treatment that mimics the effect of the protective mutation in the ARU population. As such, a treatment that mimics the mutation is less likely to have the side effects that so often derail an otherwise promising drug treatment, sometimes when clinical trials are very advanced.

11. In conclusion, I am a person of ordinary skill in this art. It is within my ability to understand and follow the claimed methods. For any disease in which the phenotype is related to a genetic difference, I would expect the claimed methods to allow someone of my skill level to discover that difference, and to correlate it with a gene-specific effect, such as a protein modification. That gene–specific effect in turn will correlate with the phenotypic difference between "at risk unaffected" (ARU) and "at risk affected" (ARA) individuals. This information will allow one skilled in the art to

design a treatment to mimic the protective phenotype of the "at risk unaffected" individuals.

I further declare that all statements made herein of my own knowledge are true and that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code.

Cammie Lesser, M.D., Ph.D.

Commonwealth of Massachusetts)
) ss.
County of Middlesex)

On this 15 day of December, 2006, before me, a Notary Public in and for the Commonwealth and County aforesaid, personally appeared Cammie Lesser, M.D., Ph.D., to me known and known to me to be the person of that name, who signed and sealed the foregoing instrument, and she acknowledged the same to be her free act and deed.

Notary Public

Commission expires 1/19/2012

STACY B. SARNO, ESQ.
Notary Public
COMMONWEALTH OF MASSACHUSETTS
My Commission Expires January 19, 2012

Cubist Pharmaceuticals Acquires Illumigen Biosciences

Expects to File IND for Lead HCV Compound IB657 in 2008

LEXINGTON, Mass. & SEATTLE -- Cubist Pharmaceuticals, Inc. (NASDAQ: CBST) and Illumigen Biosciences, Inc. announced today that Cubist has acquired Illumigen pursuant to a definitive agreement and plan of merger entered into on December 24, 2007. Illumigen's lead compound is IB657, a protein therapeutic in pre-clinical development for the treatment of Hepatitis C Virus (HCV) infections. Cubist expects that an IND for IB657 will be filed in 2008.

Pursuant to the terms of the agreement, which was approved by the Boards of Directors of each company, Cubist will pay to the Illumigen stockholders $9 Million (after adjusting for Illumigen's closing cash balance) in cash and Illumigen has become a wholly-owned subsidiary of Cubist. Cubist will make payments during the development of IB657 as a therapy for HCV infections of up to $75.5 Million upon achieving certain development and regulatory milestones. If Cubist develops Illumigen products for the treatment of viruses other than HCV, development and regulatory milestone payments of up to $117 Million could apply. Assuming that HCV or other Illumigen antiviral products are commercialized, additional milestone payments of up to $140 Million, as well as tiered royalties, could apply.

Mike Bonney, President and CEO of Cubist Pharmaceuticals, said "We are excited about the opportunity of filing an IND for IB657 in the coming year and advancing it into the clinic. An HCV product candidate is an important addition to our pipeline, and leverages our antiinfective development, regulatory, and commercialization expertise."

Donald Elmer, Chairman of Illumigen Biosciences, said "We believe that Cubist is ideally positioned to exploit the immediate opportunity for IB657 against HCV, and potentially for additional viral infections."

No financing will be necessary to complete the acquisition of Illumigen or to fund the development of IB657. The impact of any charges related to purchase accounting, including in-process R&D, will be recorded in Cubist's 2007 full-year results.

About HCV

HCV is a virus that primarily targets the liver, currently causing infection in more than 4 million people in the U.S. and 180 million people worldwide. The virus is difficult to eradicate, with infected patients eventually developing chronic liver infection, and, in some cases, liver cancer. HCV infection is the most common reason for liver transplantation in the U.S. and Western Europe and the leading cause of death from liver disease.

No vaccine is currently available to prevent HCV infection. Current HCV therapy combines a pegylated-interferon with ribavirin for up to 48 weeks of treatment. Current therapy has significant problems with both safety (e.g., significant treatment limiting adverse effects and contraindications) and efficacy (e.g., 80% of HCV infections in the U.S. are due to genotype 1 virus for which the efficacy rate of current therapy is approximately 40 to 50%). The HCV market was $2.2 Billion in 2005 and is projected to double to $4.4 Billion in 2010. This growth will be driven by an increase in the number of patients being treated, uptake of new drugs, and the use of multi-drug treatment regimens.

About IB657

IB657 is a pre-clinical protein therapeutic being developed for treatment of HCV infection. Based on its antiviral activity, IB657

may have therapeutic utility in the treatment of certain other viral diseases. Pre-clinical studies to assess activity against these viruses may occur in parallel with its development for HCV infection.

About Illumigen

Illumigen Biosciences, Inc. was co-founded by Drs. Charles Magness and Shawn Iadonato in 2000 to discover beneficial human genetic mutations that might provide a roadmap for novel therapeutic drug mechanisms. The discovery of IB657 resulted from an investigation into the cause of apparent immunity to HCV infection enjoyed by people with a specific naturally occurring genetic mutation. Prior to founding Illumigen, Drs. Magness and Iadonato both were involved in the Human Genome Project. Illumigen is a Seattle-based, privately held biopharmaceutical company financed by Pacific Horizon Ventures in Seattle, WA. Additional information can be found at Illumigen's web site at www.illumigen.com and www.pacifichorizon.com.

About Cubist

Cubist Pharmaceuticals, Inc. is a biopharmaceutical company focused on the research, development, and commercialization of pharmaceutical products that address unmet medical needs in the acute care environment. In the U.S., Cubist markets CUBICIN[R](daptomycin for injection), the first antibiotic in a new class of anti-infectives called lipopeptides. The Cubist product pipeline includes pre-clinical programs that address unmet medical need in Gram-positive infections, Gram-negative infections, and CDAD (Clostridium difficile-associated diarrhea). Cubist is headquartered in Lexington, MA. Additional information can be found at Cubist's web site at www.cubist.com.

Cubist Safe Harbor Statement

Statements contained herein that are not historical fact may be forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934, and such statements are subject to a variety of risks and uncertainties. There are a number of important factors that could cause actual results to differ materially from those projected or suggested in any forward-looking statements made by Cubist. These factors include, but are not limited to: (i) the level of acceptance of CUBICIN by physicians, patients, third-party payors and the medical community; (ii) any changes in the current or anticipated market demand or medical need for CUBICIN; (iii) any unexpected adverse events related to CUBICIN, particularly as CUBICIN is used in the treatment of a growing number of patients around the world; (iv) competition in the markets in which we and our partners market CUBICIN, including marketing approvals for new products that will be competitive with CUBICIN; (v) whether the U.S. Food and Drug Administration, or FDA, accepts proposed clinical trial protocols that may be achieved in a timely manner for additional studies of CUBICIN or any other drug candidate we seek to enter into clinical trials; (vi) whether we will receive, and the potential timing of, regulatory approvals or clearances to market CUBICIN in countries where it is not yet approved; (vii) legislative and policy changes in the United States and other jurisdictions where our products are sold that may affect the ease of getting a new product or a new indication approved; (viii) changes in government reimbursement for our or our competitors' products; (ix) whether or not third parties may seek to market generic versions of our products by filing Abbreviated New Drug Applications, or ANDAs, with the FDA, and the results of any litigation that we file to defend and/or assert our patents against such generic companies; (x) our ability to conduct successful clinical trials in a timely manner; (xi) the effect that the results of ongoing or future clinical trials of CUBICIN may have on its acceptance in the medical community; (xii) the ability of our third party manufacturers, including our single source provider of active pharmaceutical ingredient, or API, to manufacture sufficient quantities of CUBICIN in accordance with Good Manufacturing Practices and other requirements of the regulatory approvals for CUBICIN and at an acceptable cost; (xiii) our dependence upon collaborations with our partners and our partners' ability to execute on development, regulatory and sales expectations in their territories; (xiv) our ability to finance our operations; (xv) the effectiveness of our sales force and our sales force's ability to access targeted physicians; (xvi) potential costs resulting from product liability or other third

party claims; (xvii) our ability to protect our proprietary technologies; (xviii) our ability to consummate the transaction with Illumigen, (xix) our ability to develop and commercialize products based on IB657, (xx) the market for HCV products and the demand for products based on IB657; (xxi) our ability to integrate successfully the operations of Illumigen or any other business that we may acquire and the potential impact of the acquisition of Illumigen or any other future acquisition on our financial results; (xxii) our ability to discover, acquire or in-license drug candidates and develop and achieve commercial success for drug candidates; and (xxiii) a variety of risks common to our industry, including ongoing regulatory review, public and investment community perception of the industry, legislative or regulatory changes, and our ability to attract and retain talented employees.

Additional factors that could cause actual results to differ materially from those projected or suggested in any forward-looking statements are contained in Cubist's recent filings with the Securities and Exchange Commission, including those factors discussed under the caption "Risk Factors" in such filings.

Cubist and CUBICIN are registered trademarks of Cubist Pharmaceuticals, Inc.